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Non-invasive brain stimulation modalities for the treatment and prevention of opioid use disorder: a systematic review of the literature

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ABSTRACT

The U.S. is currently facing an unprecedented epidemic of opioid-related deaths. Despite the efficacy of the current treatments for opioid use disorder (OUD), including psychosocial interventions and medication-assisted therapy (MAT), many patients remain treatment-resistant and at high risk for overdose. A potential augmentation strategy includes the use of non-invasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and auricular vagus nerve stimulation (aVNS). These approaches may have therapeutic benefits by directly or indirectly modulating the neurocircuitry affected in OUD. In this review, we evaluate the available studies on NIBS in the context of OUD withdrawal and detoxification, maintenance, and cravings, while also considering analgesia and safety concerns. In the context of opioid withdrawal and detoxification, a percutaneous form of aVNS has positive results in open-label trials, but has not yet been tested against sham. No randomized studies have reported on the safety and efficacy of NIBS specifically for maintenance treatment in OUD. TMS and tDCS have demonstrated effects on cravings, although published studies were limited by small sample sizes. NIBS may play a role in reducing exposure to opioids and the risk of developing OUD, as demonstrated by studies using tDCS in an experimental pain condition and TMS in a post-operative setting. Overall, while the preliminary evidence and safety for NIBS in the prevention and treatment of OUD appears promising, further research is needed with larger sample sizes, placebo control, and objective biomarkers as outcome measures before strong conclusions can be drawn.

Introduction

The United States is currently facing an unprecedented epidemic of opioid overdoses and deaths.[1] There continue to be major public health problems due to the use of illicit opioids even as opioid prescribing guidelines and laws have become more restrictive.[2] The total economic burden from opioid abuse in the US is estimated to be $78 billion per year.[3] Opioid use disorder (OUD) is a chronic brain disease with negative consequences that include loss of control and lasting disruptions in neurocircuitry.[4,5] OUD is also highly lethal. A 33-year follow-up study reported a mortality rate of 50% in subjects meeting criteria for OUD in their 20's.[6] A staggering 399,000 people have died from overdoses involving any opioid from 1999-2017.[7] These statistics show the critical nature of the national epidemic and point to the pressing need to further the understanding of OUD and explore novel interventions to alleviate this problem.

The mechanism-of-action of opioid medications has been well studied. Their analgesic effects are mediated through binding of the mu-opioid receptor, which indirectly stimulates descending inhibitory pathways acting on the periaqueductal gray (PAG) and nucleus reticularis paragigantocellularis (NRPG). This ultimately

leads to a reduction of nociceptive signals from peripheral neurons to the thalamus. Exogenous and endogenous opioids also bind to peripheral nociceptors and exert a direct inhibitory effect.[8] Opioids engage the kappa- and delta-opioid receptors which, along with mu-opioid receptors, facilitate the many side-effects associated with opioid use. Notably, stimulation of these receptors in the brainstem induces the reduction of consciousness, and respiratory rate and airway reflexes that result in death following an overdose.[8] The addictive properties of opioids are similar to other drugs of abuse that cause release of dopamine in brain reward systems.[9] The subsequent drop in dopamine concentration has been postulated to facilitate the experience of cravings upon the cessation of opioids.[10]

Existing treatments for OUD include behavioral and pharmacological approaches. Behavioral interventions alone have high rates of relapse, approaching 80% within two years of intensive treatment.[11–13] Medication-assisted treatment (MAT) uses medications and a combination of individual and/or group psychosocial counseling.[14] Pharmacological treatments approved by the Food and Drug Administration (FDA) include the mu opioid-receptor antagonist naltrexone, agonist methadone, and partial-agonist buprenorphine.[15] There is limited research on whether a patient presenting with OUD responds better to one medication over another.[16] Unfortunately, even with MAT, there remains a high relapse rate of close to 25% after 41 months.[17] This limited efficacy suggests further treatment options are necessary.

Non-invasive brain stimulation (NIBS) technologies provide a non-pharmacologic approach to modulating brain activity. Given the discrete neural pathways affected in OUD, NIBS may offer an attractive therapeutic option.[18,19] Several NIBS modalities are FDA approved, including repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder,[20] which is highly co-morbid with OUD.[21] Transcranial magnetic stimulation (TMS) activates underlying cortical regions through fluctuating magnetic fields.[22] Repetitive TMS induces neuroplastic changes, with high-frequency (>5 Hz) traditionally viewed as excitatory, and low-frequency (1 Hz) viewed as inhibitory (though see[23] differing patterns on brain connectivity). Other NIBS techniques utilize electrical stimulation of the brain or cranial nerves, such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), external trigeminal nerve stimulation (eTNS), and non-invasive auricular vagus nerve stimulation (aVNS).

The left dorsolateral prefrontal cortex (DLPFC) is the FDA-approved TMS target for the treatment of major depressive disorder (both repetitive and theta burst TMS, a more recent approach that induces therapeutic effects with higher frequency stimulation with much shorter treatments;[24,25]) The DLPFC is viewed as an accessible entry point for targeting the cognitive control neurocircuit.[26] This neurocircuit has been shown to be functionally connected to the anterior cingulate cortex (ACC), the precentral gyrus and the dorsal parietal cortex. Aspects of this circuit, particularly the ACC and its functionally connected structures, have been shown to be dysfunctional in cravings for nicotine, food, alcohol and opioids.[27–30] The use of NIBS to target the DLPFC for cravings in SUD may be particularly important in patients with co-morbid depression because of reduced hedonic tone.[18,31]

Given the ability of NIBS to affect dysregulated neurocircuitry there may be clinical utility for these techniques in the treatment of substance use disorders. Along these lines, there have been recent reviews covering invasive neuromodulation techniques (such as deep brain stimulation) focused on opioid use disorder,[32] non-invasive brain stimulation in the context of addiction as a whole,[33] and a recent consensus paper on transcranial electrical and magnetic stimulation for addiction medicine with a focus on research methodology.[34] However, there is a lack of a focused review of non-invasive brain stimulation for opioid use disorder. Given the ongoing opioid epidemic, we focused this critical review of the literature on non-invasive brain stimulation techniques and their therapeutic potential for patients suffering with this life-threatening condition.

In this review, we evaluate the available studies using non-invasive brain stimulation modalities

in the context of opioid use disorder. We focus on non-invasive neuromodulation interventions in several clinical scenarios relevant to the treatment of OUD, including opioid withdrawal and detoxification, maintenance treatment, and the management of opioid cravings. We also examined the literature of NIBS in the context of analgesia, given that reducing exposure to opioids may also reduce the risk of developing OUD. Lastly, we consider safety concerns of brain stimulation modalities in this clinical population.

Methods

As the current literature available for non-invasive brain stimulation techniques in the context of opioid use disorder is limited, we employed a qualitative approach. All studies were identified and selected from the PubMed database. We used a broad search strategy that started with the following search criteria: "transcranial magnetic stimulation" OR "transcranial direct current stimulation" OR "Bridge device" OR "auricular vagus nerve stimulation" OR "transcranial electric nerve stimulation" AND "opioid use disorder" OR "substance use disorders." We examined all studies published before October 28, 2019. Selected studies were then examined by the authors JRY and SAS for relevance to this literature review.

Studies were included if they examined the therapeutic effects of a NIBS technology for opioid use disorder in the context of withdrawal and detoxification, maintenance treatment, cravings, as well as for analgesia. Studies were excluded if they were not completed in human subjects, did not include non-invasive brain stimulation methods, or were not relevant to OUD. Papers examining NIBS for other substance use disorders were only included in the absence of any OUD literature. Ongoing studies were also excluded. We also chose to include studies that examined mechanisms of action of NIBS in these contexts where available. We also prioritized the inclusion of studies that had outcome measures that were clinically relevant. In total, 18 studies were identified and included in this qualitative literature review (see Figure 1).

Results

NIBS during Withdrawal and Detoxification Management

Clinical opioid withdrawal syndrome is largely mediated by adrenergic hyperactivity from the locus coeruleus, and characterized by several physical and psychiatric symptoms. These include lacrimation, diaphoresis, pupil dilation, elevated temperature, hypertension, tachycardia, nausea, diarrhea, piloerection, insomnia, marked anhedonia, and can persist up to 72 hours after abstaining from opioid use.[35] Many detoxification strategies use a buprenorphine taper to reduce the severity of withdrawal symptoms, typically over a 4-week period.[36] Unfortunately, without medications, the withdrawal symptoms often lead to relapse.[37]

There is limited work studying the use of non-invasive brain stimulation modalities during opioid detoxification and withdrawal management. We identified one study of auricular vagus nerve stimulation (aVNS) for opioid detoxification and withdrawal management. aVNS devices act by stimulating the auricular branch of the vagus nerve, which projects afferents into the nucleus of the solitary tract (NTS), and subsequently affects other brain structures involved in autonomic control, pain perception, and emotion.[38]

An uncontrolled retrospective cohort trial compared the signs and symptoms of opioid withdrawal before and after percutaneous aVNS.[38] Patients were treated during medically supervised periods of intentional withdrawal from opioids. Four sterile titanium needles were implanted in the skin overlying the ear, delivering 3.2V with alternating frequencies for 5 days. Subject's clinical opioid withdraw scale (COWS) score was recorded at several intervals including a 5-day follow up visit. The mean COWS score decreased from 20 to 4 after 30 minutes of stimulation. In the 5 day follow up, patients had an average withdrawal score of less than 1 and nearly 90% of patients were able to begin medication-assisted treatment.[38] Interestingly, another study was able to find that aVNS is most effective during exhalation, which was postulated to be related to the modulation of NTS by the brainstem autonomic control centers.[39] This finding
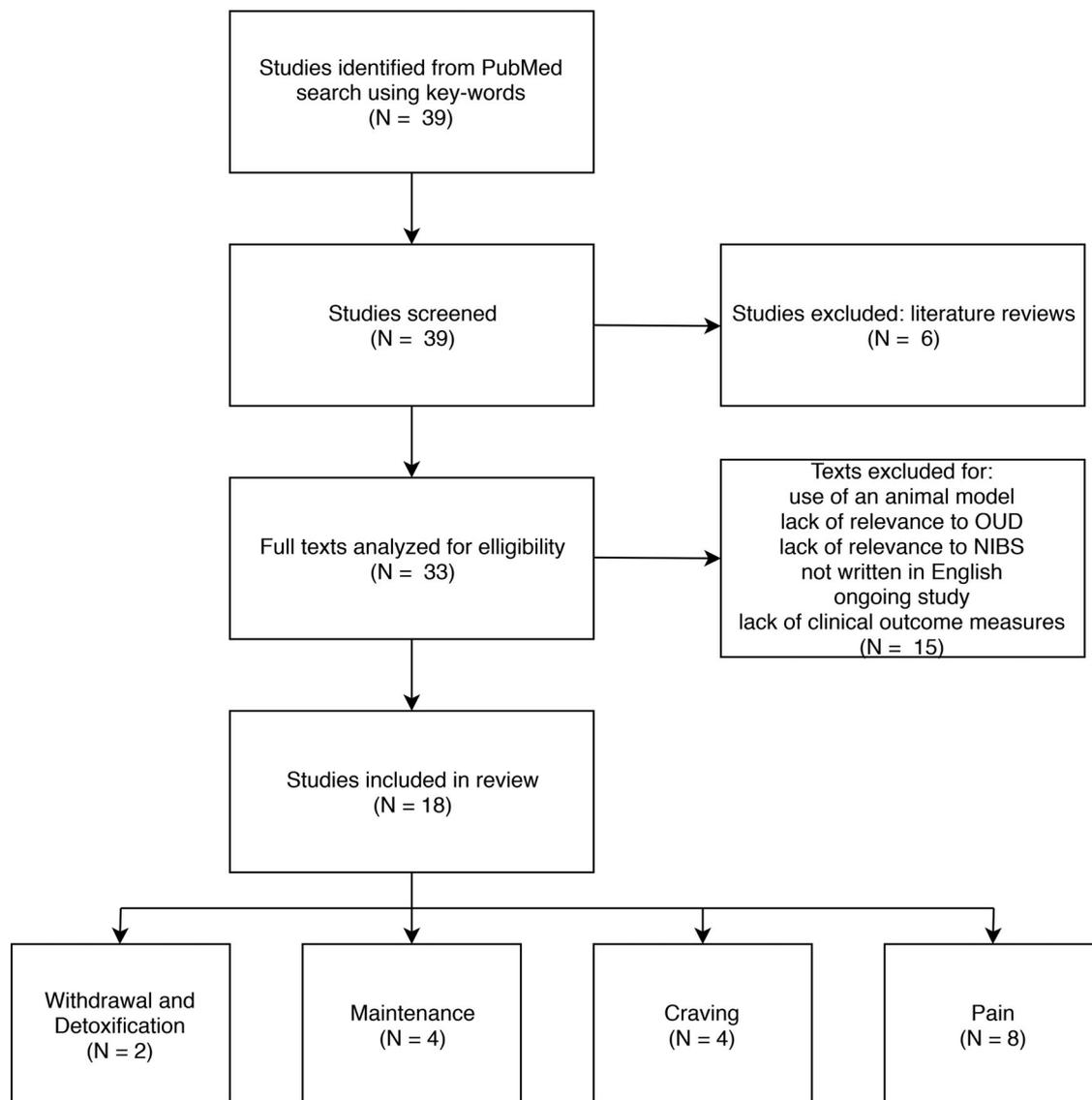
Figure 1. Research methodology flow chart.

suggests the possibility of improving the effectiveness of aVNS technologies by synchronizing stimulation with breathing pattern.

In 2017, FDA granted clearance for the NSS-2 Bridge device used in the above study for the treatment of withdrawal symptoms in opioid use disorder and the wider field of substance abuse disorder.[40] More recently, the FDA cleared another non-invasive auricular neurostimulator, Drug Relief by DyAnsys, designed to reduce opioid withdrawal symptoms.[41] Several reviews have established that aVNS contains minimal risk, though it would still be wise to examine the patient's relative risk on a case-by-case basis.[42]

We did not find studies on other non-invasive brain stimulation methods such as TMS or tDCS specifically in the context of opioid detoxification and withdrawal management. Further studies on the safety and efficacy of TMS and tDCS should be pursued in this clinical context. While preliminary trials for aVNS technologies are promising, there is a need for randomized, double-blind, sham-controlled trials.

NIBS during Maintenance Treatment

Prevention of relapse is the main goal of maintenance therapy in the treatment of OUD. As previously described, medication-assisted therapy (MAT) has demonstrated the lowest rates of relapse when compared to non-pharmacologic treatments.[37] FDA-approved medications for

relapse prevention include naltrexone, methadone, and buprenorphine. Retention rates at 1 year for methadone use is about 60%. Naltrexone has a lower retention rate than both buprenorphine and methadone, and so the long-acting injectable formulation is recommended. Unfortunately, these treatments are not without risk. The primary issue with methadone in maintenance therapy is risk of overdose when combined with illicit opioids.[37] There have also been links to cardiac complications with the use of methadone, including QTc prolongation on the electrocardiogram (ECG), which predisposes to arrhythmias such as torsade de pointes.[37] Methadone and buprenorphine both carry a risk of overdose, misuse, abuse and diversion, which have resulted in strict prescribing regulations in the context of the treatment of addiction. Although MAT provides an effective treatment, current options for long-term maintenance of opioid abstinence are limited.[37] The positive effects of NIBS during opioid detoxification suggests a similar therapeutic effect could apply during maintenance treatment. Nonetheless, there is currently no literature examining the effects of non-invasive brain stimulation in the maintenance of opioid use disorder, but application of these modalities in other substance use disorders suggest the possibility for their use in OUD and should be further studied.

A commonality of substance abuse disorders is the involvement of dopaminergic reward circuitry, which could be targeted by NIBS during maintenance treatment across SUDs including OUD. In a smoking cessation study, a double-blind, randomized, sham-controlled protocol applied 8 sessions 20 Hz TMS over the left dorsolateral prefrontal cortex (DLPFC) significantly reduced the relapse rate up to 12 weeks after treatment ($p < .01$;[43]) Another study in tobacco use disorder utilizing a within-subject, double-blind, randomized design applied 1.0 mA tDCS with the anode over the left DLPFC and cathode over the right supra-orbital area which resulted in decreased cigarette consumption ($p = .014$), with effects lasting up to 4 weeks in some patients.[44] In a cocaine use disorder population, a sham-controlled pilot study demonstrated that multiple (up to 13) sessions of 10 Hz rTMS using

the H7 coil over the left medial prefrontal cortex successfully reduced the amounts of cocaine self-administration, although this reduction was not significantly different from sham ($p = .48$;[45]) In an alcohol use disorder population, two randomized, sham-controlled trials demonstrated that 10 sessions in 5 days of 2 mA tDCS (13 minutes in the first trial, 20 minutes in the second), with cathode over the left DLFC and anode over right DLPFC, resulted in reduced relapse rates of former alcoholic patients ($p < .05$;[46,47]) Collectively, these studies provide promising evidence of the benefits of different NIBS techniques across a range of substance use disorders, while also generally pointing towards sound inferential methodologies.

As previously discussed, the mechanism underlying the addictive properties of substances of abuse lie in the dopamine pathways of the brain including mesolimbic projections form the ventral tegmental area to the ventral striatum.[10] Continued use of drugs of abuse cause downregulation of dopamine receptors, leading to the development of tolerance and the use of progressively greater doses to achieve similar effects. Given the positive benefits of brain stimulation techniques on relapse for nicotine, alcohol, and cocaine use disorders, there may be a similar effect on relapse rates in patients undergoing maintenance for opioid use disorder. Future studies should continue to build on these successes to test such NIBS interventions within the context of maintenance treatment of OUD.

NIBS for Cravings

The subjective desire to use opioids after cessation plays a large role in relapse. The personal experience of craving is variable but thought to be mediated by incentive sensitization in the mesolimbic dopamine pathway, creating a larger incentive salience to the drug of abuse.[48] When viewing a drug cue, altered neurocircuitry results in a pathological activation of mesolimbic structures such as the ventral striatum, with dopamine release in turn strengthening the subjective experience of craving.[48] There have been several studies examining the effects of various noninvasive brain stimulation modalities on the craving

of opioids, which may play a role in the prevention of relapse.

One randomized, sham-controlled study examined the effects of rTMS over the left DLPFC on cravings induced by heroin cues in 20 subjects suffering from chronic OUD.[49] In this study, 20 male heroin addicts were given daily 10 Hz rTMS over 5 days (train duration 5 seconds, intertrain interval 10 seconds). Patients viewed videos of heroin use and reported their subjective heroin craving score on a scale of 1 to 100 at baseline and after each rTMS session. By the end of the 5th session, patients reported craving scores that were on average 20 points lower than their initial craving scores at baseline (p = 0.015). An additional 4 days of treatment reduced craving scores even further in the active TMS group. This clinical improvement in cravings was postulated to be secondary to changes to the dopaminergic circuitry through DLPFC activation.[49] Left DLPFC 10Hz rTMS has been shown to reduce craving for other substances of abuse as well as for behavioral addictions such as gambling in similarly designed studies (Gay et al., 2017; Li et al., 2013), but not all (Sauvaget et al., 2018). Results may be confounded by nonspecific placebo or time effects. Given the reduction in cravings for multiple substances, this suggests a general mechanism of left DLPFC stimulation to reduce a sensitized reward pathway rather than specific effects on the neurochemical pathways altered by a given drug of abuse or behavioral addiction.

A case study of a 25-year-old patient with co-occurring cocaine use disorder and opioid use disorder provides further, although anecdotal, evidence that rTMS can decrease cravings in opioid dependent patients. In this study, the patient was given 10 Hz rTMS over left DLPFC at 100% motor threshold for a duration of 10 minutes each session, total of 7 sessions in 3 weeks. Cue-induced craving was measured on a 100-point visual analog scale. Ten minutes after each rTMS session, heroin craving scores fell on average from 68.6 to 14.3.[50]

Another randomized, controlled study evaluated tDCS targeting the frontal-parietal-temporal (FPT) area on heroin craving symptoms.[51] Stimulation was administered to 20 patients during a single session at 1.5 mA over 20 minutes. Two cathodes were placed over the bilateral FPT and anodes was placed over the occipital lobe. Similar to the previously mentioned TMS study, craving scores were evaluated on a scale after subjects watched a video of heroin use. Craving scores were recorded at baseline (on a subjective scale of 0-100) and after the single session of tDCS. A significant reduction in the craving scores after heroin cues were demonstrated, but active did not separate from sham stimulation, which may have been due to low statistical power.[51]

A relatively larger study examined the role of tDCS in attenuating cravings for opium. In this randomized, controlled preliminary study of 60 subjects, cathode stimulation was placed over the left DLPFC and anode stimulation over the right DLPFC.[52] Study groups included a control group with sham tDCS and methadone treatment, an experimental group with active tDCS plus methadone maintenance treatment, and a group with only methadone maintenance treatment. tDCS was administered at 2 mA for 20 minutes, 1 session per day for 10 consecutive days. Subjects reported their subjective drug craving scores using the Desire for Drug Questionnaire and the Obsessive-Compulsive Drug Use Scale one week before and one week after treatment. When compared to the other two groups, the active tDCS group had a significant reduction on average craving scores (partial η effect size = 0.48, p=.0001). This study suggests that tDCS in combination with a medication-assisted treatment, such as methadone, could be an effective strategy in reducing cravings for opioid use.

Based on the studies outlined above, there is some evidence to suggest NIBS approaches have an impact on the cravings for opioids. These studies are limited in their generalizability by small sample sizes and nonspecific effects. One study was also non-significant in terms of stimulation effects on craving scores, although treatment was with only a single tDCS stimulation session.[51] Nonetheless, these studies provide preliminary evidence of non-invasive brain stimulation techniques affecting cravings and their feasibility during OUD treatment.

NIBS to Reduce Opioid Exposure in Pain Conditions

A potentially impactful use of non-invasive brain stimulation may be as a post-operative analgesic.

As previously mentioned, the clinical administration of opioids in the context of pain management has contributed to the development OUD in many individuals.[9] To limit iatrogenic factors of the development of OUD, strategies for pain management that carry less risk of addiction are desired. Several NIBS techniques including tDCS and TMS have been found to be useful in pain management and may offer a means to curb acute opioid use. We identified six pivotal trials and their significance to the use of NIBS as an analgesic.

Five studies examined the role of tDCS as an analgesic and its effect on post-operative opioid requirements. One was a double-blind, randomized, controlled trial applying tDCS over the motor or prefrontal cortices to evaluate reduction in pain scores following total knee arthroplasty (TKA).[53] Subjects (n = 58) were randomly assigned to 4 groups: motor, prefrontal, active-control, and sham. The anode/cathode electrodes were placed at motor/right prefrontal cortices, left prefrontal/right sensory cortices, left temporal-occipital junction/medial-anterior-premotor area. Subjects received four 20-minute sessions of tDCS at 2 mA, two on post-op day-0 separated by 4 hours, and two on post-op day-1 also separated by 4 hours. Patient-controlled analgesia (PCA) use was tracked for 72 hours following surgery. Interestingly, subjects in the prefrontal stimulation group had significantly less PCA hydromorphone use compared to sham (p < 0.0001); however, subjects in the motor stimulation group used significantly more PCA hydromorphone than sham (p < 0.0001). In a similar post-operative pain control study in patients receiving unilateral TKA (n = 50), tDCS was administered in four 20-minute sessions of 2mA tDCS over 4 consecutive days, with the anode placed over primary motor cortex and the cathode over the ipsilateral arm. In this study, the total does of nalbuphine post-TKA was significantly lower (p < .001) in the active stimulation group than sham after the second session.[54]

In a third study, a double-blind, randomized, and sham-controlled intervention examined the analgesic effect of tDCS in patients who had undergone lumbar spine surgery, a procedure that typically results in significant pain scores in the acute post-operative period.[55] The anodal electrode was positioned over the left DLPFC and the cathode electrode was positioned on the scalp over the right ear. Stimulation was given at 1 mA with fade in/out every 8 seconds. The single session lasted 20 minutes. Results showed no significant differences in pain or mood scores between sham and experimental groups over two days. Possible reasons for the lack of a statistically significant effect include a relatively low current compared to other studies (1mA vs 2 mA) and that only a single stimulation session was administered.

Another pilot study compared hot/cold pain thresholds in 9 healthy subjects after a single session sequential placebo then active tDCS at 2 mA. The anode was placed over the right motor cortex and cathode over the left supraorbital region. Using Quantitative Sensory Testing, statistically significant differences were demonstrated in left face heat (p = 0.032) and cold (p = 0.012) pain thresholds throughout the experiment.[56] Another randomized, sham-controlled pilot study examined the feasibility of a single session of 2 mA tDCS in 21 subjects post-endoscopic retrograde cholangio-pancreatography. Here the anode electrode was placed over the left prefrontal cortex and the cathode electrode over the gut representation of the right sensory cortex. Results demonstrated that active tDCS produced a 22% decrease in hydromorphone use compared to sham stimulation (p = .0003;[57])

Three studies were identified that examined the role of TMS as a potential analgesic. One was a case report of a 71-year-old woman who presented with clinical evidence of central sensitization of pain associated with left knee osteoarthritis.[58] In this case, rTMS was administered at 10 Hz delivered to the right motor cortex (80% MT) once monthly for 10 months. By the 10th session, pain was reduced by approximately 67%. While anecdotal, this case report may support the feasibility that rTMS could be a therapeutic option for individuals suffering from neuropathic pain.

Compared to the previous TMS study in which a clinical application was reported, others aimed to explain the mechanism of the analgesic effects of this modality. One study using a prospective,

randomized, sham-controlled, double-blind, crossover design evaluated whether left DLPFC rTMS-induced analgesia was sensitive to mu opioid receptor blockage.[59] Subjects underwent a single rTMS treatment over the DLPFC at 10 Hz stimulation over 20 minutes. Healthy volunteers (n = 24) received active or sham TMS after either intravenous saline or naloxone infusion, a non-selective and competitive opioid receptor antagonist. Subjects were then exposed to acute hot and cold pain in a randomized and sequential fashion, and pain scores were measured using Quantitative Sensory Testing. Opioid receptor blockade via naloxone infusion significantly reduced the analgesic effects of active stimulation, suggesting that the mechanism of rTMS-induced analgesia is related to the release of endogenous opioids.

Another experimental pain rTMS study evaluated the role of neurotransmitters in pain relief using positron emission topography (PET). This study recruited healthy human subjects (n = 10) and administered rTMS at 10 Hz, 90% motor threshold, total 1000 pulses. Consistent with the previous study, rTMS was found to activate the endogenous opioid system. Structures activated included the right ventral striatum, medial orbitofrontal, prefrontal and anterior cingulate cortices, left insula, dorsolateral prefrontal cortex, superior temporal gyrus, and precentral gyrus, all of which are involved in the modulation of experimentally induced thermal pain. No significant change in dopamine D2 receptor availability was found, which is consistent with a lack of long-term dopamine release.[60] This suggests that rTMS does not cause receptor sensitization similar to drugs of abuse.

Reducing exposure to opioid medications may play a large role in preventing the development of opioid use disorder. The application of NIBS modalities such as TMS and tDCS appear to reduce opioid requirements in the context of post-operative pain and potentially in other pain syndromes. Treating both acute and chronic pain syndromes with NIBS may ultimately play an important role in mitigating the opioid crisis. As this literature has continued to mature, there are now sufficient studies to calculate meta-analytic effect sizes which ultimately could help identify moderators of these effects and assure against potential under reporting of null findings.

Risks of NIBS in the Treatment and Prevention of OUD

An important consideration in any treatment intervention is the risks and costs associated with a therapy. In the case of NIBS the risks of treatment are fairly limited as compared to the potential systemic adverse effects associated with pharmacotherapy. However, in the context of substance use disorders and pain conditions, the risk of side effects by NIBS may be increased. In particular, medications or illicit substances that lower seizure threshold increase the risk of accidental seizures induced by brain stimulation.[61] As there have been reported cases of TMS-induced seizures in patients with substance use disorders,[62] such risks cannot be discounted. However, beyond seizure induction, no evidence has been reported for increased risk of serious adverse events caused by NIBS in the context of OUD. As such, and as highlighted in the recent consensus statement on NIBS for substance use disorders[34] it is unnecessary that current NIBS protocols should be modified for safety considerations.

Limitations

There are several potential limitations to this systematic review that must be addressed. Originally 46 papers were considered for this review, with 7 of them being rejected initially. After screening for inclusion and exclusion criteria, only 20 papers were identified for this study. As such, this is a relatively small literature to consider. Moreover, the research addressing NIBS for OUD is developing rapidly and therefore more new information should be expected in the near future that may change the prevailing views on this topic. Nonetheless, this review constitutes a comprehensive survey of the current state-of-the-art. Despite this, there are important gaps that remain unfilled. For example, as previously mentioned, there is currently no literature examining the efficacy of NIBS for OUD maintenance treatment. Clearly, this is not ideal and it is crucial

Table 1. Studies on non-invasive brain stimulation for opioid use disorder

Setting	Author	Study design	Study population	n	Modality	Stimulation parameters	Outcome measures	Follow up	Results
Detoxification & Withdrawal Management	38	Retrospective, open-label cohort	Patients in acute opioid withdrawal	73	percutaneous aVNS (Bridge device)	3.2V continuous with alternating frequencies for 5 days	COWS	Baseline, 20 min, 30 min, 1 hr, and 5 days post-placement	Mean COWS score decreased from 20 to 7 after 20 minutes, then to 0.6 after 5 days. Nearly 90% were able to beging MAT
	39	Sequential, sham-controlled	Healthy controls	25	aVNS	25 Hz, pulse duration 1 s, biphasic rectangular pulse trains, 450 microsecond pulse width	evoked fMRI	During stimulation	aVNS had greatest effect on evoked fMRI signal during exhalation at the ipsilateral pontomedullary junction (including NTS), locus ceruleus, dorsal and median raphe nuclei
Maintenance Treatment	46	Randomized, sham-controlled	Alcohol-dependent patients	33	tDCS	2 mA for 13 min, two sessions daily, 20-min interval, 5 consecutive days, total 10 sessions, cathode over left DLFC, anode over right DLPFC	5-item obsessive compulsive drinking scale; relapse rates	Baseline, weekly in the first 4 weeks, then monthly for 5 months	At 6 months, 50% relapsed in active group compared to 88% in sham group (p = 0.021)
	45	Randomized, sham-controlled, pilot	Cocaine-dependent patients	18	rTMS	10 Hz, H7 coil, left MPC, 90–110% MT, train duration 3 s, 40 train duration, inter-train interval 20 s, total 1,200 pulses; or 1 Hz, 900 pulses; up to 13 sessions	Cocaine self-administration	Baseline, then at 4 days and 13 days	Reduced amounts of cocaine self-administration, not significantly different from sham (p = .48)
	43	Randomized, double-blind, sham-controlled	Tobacco smokers	29	rTMS	20 Hz, figure-of-8 coil, left DLPFC, 110% MT, 1s train duration, inter-train interval 20 s, 900 pulses, 16 min, 8 sessions over 2 weeks	Rate of relapse	Baseline, after each session, then at 4, 8, and 12 weeks	Significantly reduced the relapse rate up to 12 weeks after treatment (p < .01)
	47	Randomized, double-blind, sham-controlled	Alcohol-dependent patients	45	tDCS	2 mA for 20 min once daily, every other day, total 10 sessions, cathode over left DLFC, anode over right DLPFC	5-item obsessive compulsive drinking scale; relapse rates	Baseline, weekly in the first 5 weeks, then at 3 months	At 3 months, 27.3% relapsed in active group compared to 72.7% in sham group (p = .01)
Cravings	49	Randomized, sham-controlled	Heroin-dependent patients	20	rTMS	10 Hz figure-of-eight coil over left DLPFC, 100% MT, 5 s train duration, 10 s inter-train interval, daily for 5 days	VAS	Baseline, 1 day, and 5 days	Craving score reduced on average 20 points lower than baseline after 1st session (p = 0.015). An additional 4 days of treatment reduced craving scores further
	51	Randomized, sham-controlled	Heroin-dependent patients	20	tDCS	1.5 mA, 20 min, single session, cathodes over right and left FPT, anodes over left and right occipital lobe	VAS	Baseline and after stimulation	Significant reduction in craving scores after heroin cues (p = .003), although ANOVA analysis revealed no significant difference between sham and active stimulation
	52	Randomized, sham-controlled	Opium-dependent patients	60	tDCS	2 mA, 20 min, 1 session daily for 10 consecutive days, cathode over left DLFC, anode over right DLPFC	Desire for drug questionnaire, obsessive-compulsive drug use scale	Baseline and 10 days	Active tDCS + methadone group had a significant reduction on average craving scores compared to control groups (sham + methadone, methadone only) (p = 0.0001)

			n	Modality	Parameters	Measure	Timing	Results
Pain								
50	Case report	25 year-old Caucasian male with co-occurring OUD and cocaine use disorder	1	rTMS	10 Hz, figure-of-eight coil, left DLPFC, 100% MT, 5 s train duration, 10s inter-train interval, 10 min sessions, 2000 total pulses; 7 sessions over 3 weeks	VAS	Baseline, 5 min, and 10min	Significant reduction in craving scores after heroin cues, averaging from 68.6 to 27.1 immediately post-rTMS, then 18.6 after 5 min, then 14.3 after 10 min
57	Randomized, sham-controlled, pilot study	Patients undergoing ERCP	21	tDCS	2 mA, 20 min, single session; anode over the right motor cortex, cathode over left supraorbital region	VAS, PCA hydromorphone use	Hourly for 24 hours	VAS not significantly different, active tDCS significant 22% decrease in hydromorphone use (p < .0003)
59	Randomized, double-blind, sham-controlled, crossover	Healthy controls	24	rTMS	10 Hz, figure-of-eight coil, left DLPFC, 110% MT, 5 s train duration, 10s inter-train interval, 20 min, single session, five min after saline or naloxone infusion	Quantitative sensory testing	Baseline, 0, 20, and 40 min after stimulation	Naloxone infusion significantly reduced analgesic effects of active stimulation (p < .05)
55	Randomized, double-blind, sham-controlled	Post-lumbar spine surgery	59	tDCS	1 mA, fade in/out every 8 sec, 20 min, single session, anode over left DLPFC, cathode on the scalp over right ear	VAS, PCA morphine use	Days 1 and 2	No significant differences in pain scores between sham and experimental groups
56	Blinded, sham-controlled preliminary study	Right-handed healthy controls	9	tDCS	2 mA, 20 min, single session, anode over right motor cortex, cathode over left supraorbital region	Quantitative sensory testing, PET	Immediately post-stimulation	Statistically significant increase in pain threshold for hot and cold stimuli (p = .012).
60	Double-blind, randomized study	Healthy controls	10	rTMS	10 Hz, figure-of-eight coil, right S1/M1 cortex representing face, 90% MT, 5 s train-duration, 10s inter-train interval, 90 % MT, 1000 pulses, single session	PET	During stimulation	Structures activated included the right ventral striatum, medial orbitofrontal, prefrontal and anterior cingulate cortices, left insula, DLPFC, superior temporal gyrus, and precentral gyrus
54	Double randomized, sham-controlled trial	Patients in the post-operative setting following TKA	50	tDCS	2 mA, 20 min, daily for 4 consecutive days, anode over M1, cathode over ipsilateral shoulder	Opioid use	Daily for 4 days	Total dose of nalbuphine was significantly lower in active versus sham from day 2 to 4 (p < .001)
53	Randomized, double-blind, sham-controlled	Post-TKA	58	tDCS	2 mA, 20 min, 4 sessions over post-op day 1 and 2, anode/cathode at motor/right prefrontal cortices, left prefrontal/right sensory cortices, or left temporal-occipital junction/medial-anterior-premotor area	PCA hydromorphone use	Through 72 hours	Prefrontal stimulation significantly less PCA hydromorphone use compared to sham (p < 0.0001); motor stimulation significantly more PCA hydromorphone than sham (p < 0.0001)
58	Case report	71 year-old femal with central sensitization of pain associated with left knee osteoarthritis	1	rTMS	10 Hz, figure-of-eight coil, right motor cortex, 80% MT, 7 s train duration, 55 s inter-train interval, 1,400 pulses, once monthly for 10 months	VAS	Monthly for 10 months	Pain scales improved by 3rd session, reduced by 67% at 10th session

Key: Auricular vagus nerve stimulation (aVNS), Clinical Opioid Withdrawal Scale (COWS), visual analogue scale (VAS) medication-assisted therapy (MAT), transcranial direct current stimulation (tDCS), repetitive trans-cranial magnetic stimulation (rTMS), functional magnetic resonance imaging (fMRI), nucleus tractus solitarii (NTS), dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPC), motor threshold (MT), fronto-parietal-temporal (FPT), opioid use disorder (OUD), total knee arthroplasty (TKA), patient-controlled analgesia (PCA), positron emision topography (PET), primary motor cortex (M1), endoscopic retrograde cholangiopancreatography (ERCP).

that future studies examine this context. Hopefully, continued research in this field will be able to provide a more robust evaluation on the efficacy of several different NIBS modalities in the different contexts of opioid use disorder. It is also important to note that this literature review was conducted solely with the use of the PubMed database, and limited to English language reports. As such, some relevant studies may have been missed.

Conclusion

Non-invasive brain stimulation modalities appear to offer a novel treatment method for opioid use disorder. Studies using TMS, tDCS, and aVNS have demonstrated some preliminary and limited evidence for the treatment of opioid withdrawal, cravings and potentially pain syndromes that may contribute to the development of OUD (see Table 1 for summary). While the current gold standard intervention involves the use of medication-assisted treatment with psychosocial therapies, adjunctive brain stimulation techniques may play a role in reducing relapse and the risks associated with MAT. Moreover, there appears to be a robust and growing literature on NIBS approaches to reduce opioid exposure in pain conditions, which point to multiple uses for these approaches. Since the majority of the literature involving non-invasive brain stimulation in opioid use disorder is limited by generalizability and small sample sizes,[63] additional research using robust study designs are indicated. There is a critical need for adequately-powered, prospective, randomized, sham-controlled trials to further assess safety, efficacy and tolerability in these patient populations. The addition of NIBS to the prevention and treatment of opioid use disorder has the potential to make a significant impact on the opioid crisis and therefore, we expect this literature to continue to grow over the near future.

Competing interests

AAP serves as a consultant and advisory board member for US World Meds, Alkermes and Indivior. JRY, SAS, NAM, MDK and LGA report no conflicts of interest.

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