Systematic Review

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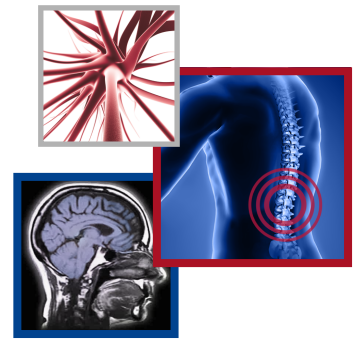
**Pain Management**



# Transcranial direct current stimulation to prevent and treat surgery-induced opioid dependence: a systematic review

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Opioid misuse leading to dependence is a major health issue. Recent studies explored valid alternatives to treat pain in postsurgical settings. This systematic review aims to discuss the role of transcranial direct current stimulation (tDCS) in preventing and treating postoperative pain and opioid dependence. PubMed and Embase databases were screened, considering studies testing tDCS effects on pain and opioid consumption in surgical settings and opioid addiction. Eight studies met our inclusion criteria. Results showed a reduction of postoperative pain, opioid consumption and cue-induced craving following cortical stimulation. Despite the limited number of studies, this review shows preliminary encouraging evidence regarding the analgesic role of tDCS. However, future studies are needed to further investigate the application of tDCS in postsurgical settings.

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The opioid crisis is arguably one of the most serious public health problems of our time. One of their main prescription uses is in the postsurgical setting. However, misuse leading to opioid dependence, and eventually to overdose death, has raised concerns regarding the impact of opioid use on public health. In 2015, over 33,000 deaths from opioid overdose were reported in the USA (63.1% of all drug overdose deaths) [1]. Epidemiological studies have shown that this rate has increased since the year 2000 [2]. Alarmingly, this rise of deaths from overdose is paralleled by the increasing rate of opioid prescriptions. Patients undergoing surgery are four-times more likely to be discharged with an opioid prescription than other patients. This major public health issue seems to be confined to the USA, which is by far the world leader in opioid consumption [3]. There is evidence of a strong relationship between the amount and duration of prescriptions and subsequent opioid misuse in the surgical population. About 1% of patients receiving opioids in a postsurgical setting will indeed develop dependence. Interestingly, the duration of prescription has more of an impact on the risk to develop dependence than the doses themselves [4]. Opioids being overprescribed by physicians appear as a serious contributing factor to the overdose mortality rate [5]. Alternatives to manage pain appropriately therefore are indeed crucial to tackle this major crisis and to improve patients' care.

The most common strategy to face opioid dependence is a pharmacological intervention (for a review, see [6]). Mainly, the methadone maintenance treatment, consisting of daily administration of the oral opioid agonist methadone, is a well-established and cost-effective treatment [7–9]. Recently some alternatives have been effectively tested, such as longer-acting agonist lambda-α-acetylmethadol and the mixed agonist/antagonist buprenorphine [10]. However, the effectiveness variability, restricted admissions in treatment programs, high rates of relapse, presence of several side effects as well as the high risk of mortality linked to methadone overdose interfere with the dependence recovery [11–15]. In addition, the mechanisms of these drugs may be diffuse. In fact, dependence mechanisms involve different dopaminergic structures, which are all part of the reward system: the prefrontal cortex, the ventral tegmental area and its projections to the nucleus accumbens [16]. While pharmacological treatments are showing

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their limits, new therapeutic options that are more targeted to the dysfunctional neural circuits are being explored, such as noninvasive brain stimulation [17,18].

Transcranial direct current stimulation (tDCS) is a technique of noninvasive brain stimulation that has already shown its efficiency in drug-avoiding behavior [19,20]. TDCS can be used to inhibit craving behavior or to control pain, depending on the area of stimulation, thus treating and preventing opioid dependence, respectively. Initial neurophysiological findings have shown bidirectional, time- and polarity-dependent excitability changes following the administration of weak electrical currents to the brain [21,22]. TDCS transiently modifies spontaneous cortical excitability by delivering low-intensity electrical currents to the scalp. Anodal stimulation depolarizes neurons' resting membrane potentials, enhancing neural excitability, while cathodal stimulation causes the opposite effect [21,23,24]. In addition to those effects that occur during and immediately after the stimulation, tDCS also results in prolonged effects that involve NMDA receptors as well as long-term potentiation and long-term depression mechanisms [21,25]. Thus, tDCS can be used to induce long-lasting modulation on neural areas associated with addiction and pain.

Regarding addiction, several studies demonstrated that single or repetitive tDCS sessions applied over the prefrontal cortex significantly reduced cue-provoked smoking and crack-cocaine craving [19,26–29] as well as alcohol craving [30]. Prefrontal stimulation can also affect the activity of the limbic system, modulating the emotional components of pain [31,32]. For pain management, the primary motor cortex is a popular target for tDCS stimulation [31,33–37]; it is hypothesized to change the activity of the thalamus [32,38,39] and pain pathway areas [23] as well as inhibit the somatosensory cortex [40–42]. Moreover, several studies demonstrated the impact of serotonin as a pain relief agent [43,44] and the role of the opioid system in the analgesic mechanism of tDCS [45,46].

In this review, we discuss the potential of tDCS to combat the opioid epidemic by reviewing its use to: first, prevent opioid addiction by using tDCS as a presurgical procedure; or in the immediate postsurgical period, and second, treat opioid addiction while using opioids.

## Methods

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols [47,48].

### Search strategy & eligibility criteria

We performed two different searches to discuss tDCS as a tool to prevent and treat postoperative pain and opioid dependence. The strategies shown in Appendix 1 were used to collect records from PubMed and Embase. We considered the following eligibility criteria: clinical trials, defined by the NIH as "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes" [49]; studies performed in humans; studies with tDCS and surgery or tDCS and opioid dependence; single or multiple tDCS sessions; studies with validated outcome measures; papers published in English; papers published after 2000; and peer-reviewed papers.

### Screening & selection of records

After identifying and excluding duplicates, two researchers performed independent filters based on title and abstract. When title/abstract lead to exclusion of the paper, the investigator used labels to justify the reason of exclusion. To ensure the blinding of the process, we used Rayyan, a web and mobile systematic reviews manager [50]. At the end of this process, the blind mode was turned off and conflicts were solved by a third evaluator. The included papers were reviewed and screened based on the inclusion and exclusion criteria.

### Data extraction

Data were extracted using two structured checklists, one for 'tDCS to prevent and treat postoperative pain' and the other for 'tDCS to treat opioid dependence'. Both of them included the following variables: bibliographic details of papers (author, title of study, journal, year and country); trial characteristics (design, duration, number of follow-ups, eligibility criteria, limitations and adverse events reported); subjects' demographics (number of participants, age and gender); tDCS parameters (device, montage, number of sessions and frequency, stimulation duration, current intensity, electrodes size); the primary and secondary outcomes measures; and results. For the 'tDCS to prevent and treat postoperative pain' search, we also considered the type of surgery and opioid used during the

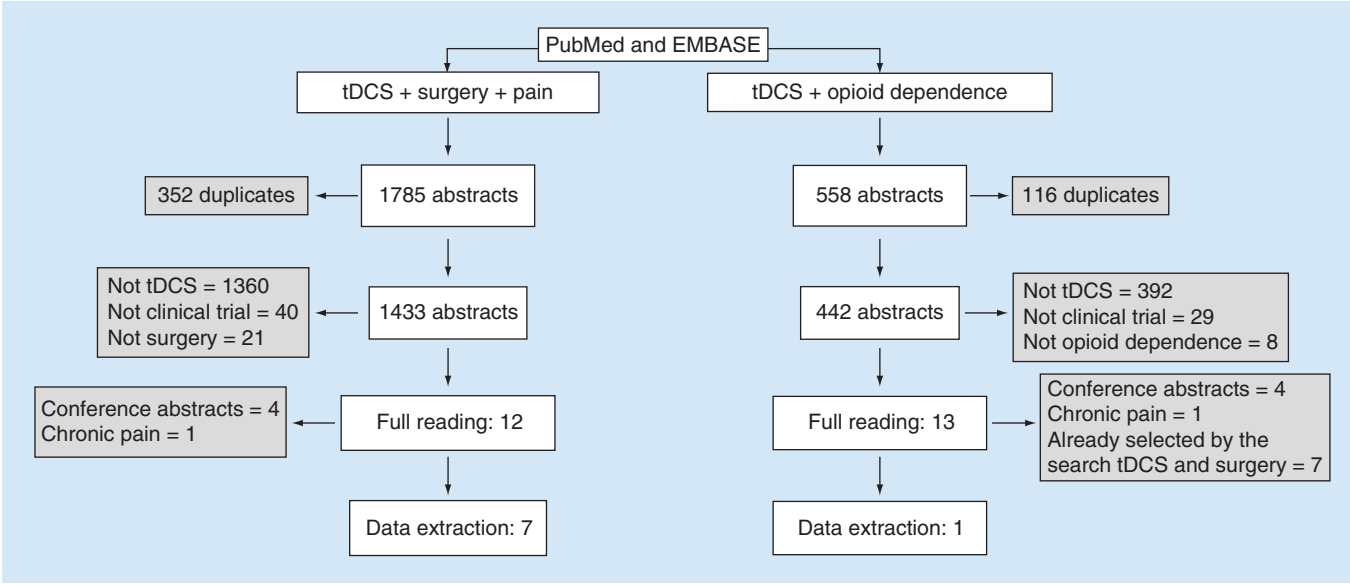


**Figure 1. Flowchart showing the selection process of papers.** The right side of the flowchart represents the selection process related to the search 'transcranial direct current stimulation to prevent and treat postoperative pain' while the left represents the search process of 'transcranial direct current stimulation to treat opioid dependence'. Gray boxes indicate papers excluded during the filtering process.

postoperative period. For the 'tDCS to treat opioid dependence' search, we added the kind of opioid prescribed and the mean of dependence time.

## Results

The search 'tDCS to prevent and treat postoperative pain' retrieved 1785 papers (455 from PubMed and 1330 from Embase). After excluding the duplicates, selecting the papers considering title and abstract, and solving the conflicts, 12 papers were included to the full reading. Among them, five studies were excluded (four conference abstracts and one related to chronic pain) and seven papers were included to the data extraction. Regarding the search 'tDCS to treat opioid dependence', 558 abstracts were collected (153 from PubMed and 405 from Embase). After the first filter process, 13 papers were selected for the full reading. Among them, we excluded 12 papers (four conference abstracts, one related to chronic pain and seven that had already been selected by the search tDCS and surgery pain). The results of the search strategy are summarized in Figure 1.

### Results 'tDCS to prevent & treat postoperative pain'

We evaluated seven clinical, randomized and sham-controlled trials [51–57]. Two of them used a single-blinded design [53,54] and five were double-blinded [51,52,55–57]. Four studies were done in the USA [53–56] while the other three were carried out in Brazil [57], Egypt [52] and Belgium [51]. The papers were published between 2011 and 2017.

The studies included 292 subjects in total. The mean age ranged from 37 to 67 years and 195 subjects (66.8%) were female. A total of 147 subjects were submitted to total knee arthroplasty, 86 to lumbar spine surgery, 40 to hallux valgus surgery and 19 to endoscopic retrograde cholangiopancreatography. Thus, the types of surgeries varied significantly across studies.

The strategy of stimulation also varied significantly across these studies; we can divide them into two main categories: stimulation of the motor cortex (four studies); and stimulation of the prefrontal cortex (two studies). One study tested both strategies in a four-group design (motor cortex vs dorsolateral prefrontal cortex vs control site vs sham) [55]. One important point to mention is that the studies utilizing primary motor cortex (M1) stimulation differed in respect to the return electrode: contralateral supra-orbital area (one study), contralateral dorsolateral prefrontal cortex (DLPFC) (two studies) and extracephalic (one study). Most of the studies used anodal polarity over the M1. For the DLPFC strategy, one study [54] placed the reference electrode at contralateral somatosensory cortex, whereas another study [51] placed the reference electrode on the scalp over the right ear in both conditions (Table 1).

Table 1. General characteristics of selected papers related to the search 'transcranial direct current stimulation to prevent and treat postoperative pain'.

| Study | Year | Sample size | Gender (male/female) | Study design | Blinding | Number of tDCS sessions | Stimulation | | Montage | | Surgical intervention | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Time | Intensity | Anode | Cathode | | |
| Borckardt *et al.* | 2011 | 19 | 0/19 | RCT | Single blinded | 1 | 20 min | 2 mA | Left DLPFC (F3) | Right sensory cortex | ERCP | [54] |
| Borckardt *et al.* | 2013 | 39 | 10/29 | RCT | Single blinded | 4 | 20 min | 2 mA | Motor area (C1 or C2) | Right DLPFC (F4) | TKA | [53] |
| Borckardt *et al.* | 2017 | 58 | 27/31 | RCT | Double blinded | 4 | 20 min | 2 mA | Left DLPFC (F3) | Sensory cortex (FPz) | TKA | [55] |
| | | | | | | | | | Motor cortex (C1 or C2) | Right DLPFC (F4) | | |
| | | | | | | | | | Left temporal-occipital junction (P3) | Medial anterior premotor area (FCz) | | |
| Dubois *et al.* | 2013 | 59 | 27/32 | RCT | Double blinded | 1 | 20 min | 1 mA | Left DLPFC (F3) | On the scalp over the right ear | Lumbar spine surgery | [51] |
| | | | | | | | | | On the scalp over the right ear | Left DLPFC (F3) | | |
| Glaser *et al.* | 2016 | 27 | 10/17 | RCT | Double blinded | 4 | 20 min | 2 mA | Superior motor cortex (Cz) | Right DLPFC (F4) | Lumbar spine surgery | [56] |
| Khedr *et al.* | 2017 | 48 | 21/27 | RCT | Double blinded | 4 | 20 min | 2 mA | Motor cortex (C1 or C2) | Ipsilateral arm (extracephalic) | TKA | [52] |
| Ribeiro *et al.* | 2017 | 40 | 0/40 | RCT | Double blinded | 2† | 20 min | 2 mA | Left motor cortex (C1) | Right supra orbital region (FP2) | Hallux valgus surgery | [57] |

Table shows the general characteristics and parameters of stimulation of each included paper.
† Before surgery.
Cz: Vertex; DLPFC: Dorsolateral prefrontal cortex; ERCP: Endoscopic retrograde cholangiopancreatography; F3: Left dorsolateral prefrontal cortex according to the 10–20 EEG system; FCz: Medial anterior premotor area according to the 10-20 EEG system; FPz: sensory cortex according to the 10-20 EEG system; mA: Milliamperes; RCT: Randomized controlled trial; tDCS: Transcranial direct current stimulation; TKA: Total knee arteroplasty.

Table 2. Results of selected papers related to the search 'transcranial direct current stimulation to prevent and treat postoperative pain'.

| Study | Year | Sample size | Pain | | | Ref. |
|---|---|---|---|---|---|---|
| | | | VAS at rest | VAS dynamic | PCA | |
| Borckardt *et al.* | 2011 | 19 | No differences (arithmetic advantages toward stimulation group) | – | 22% less ($p = 0.0003$) | [54] |
| Borckardt *et al.* | 2013 | 39 | No differences | – | 46% less ($p = 0.006$). ES = 0.95 | [53] |
| Borckardt *et al.* | 2017 | 58 | No differences | – | Anode over F3 vs sham: 24% less ($p < 0.0001$). ES = 0.365 | [55] |
| | | | | – | Anode over M1 vs sham: 27% more ($p < 0.0001$). ES = -0.323 | |
| | | | | – | Anode over P3 vs sham: no differences | |
| Dubois *et al.* | 2013 | 59 | F3 cathodal vs sham: 43% less ($p = 0.150$) | F3 cathodal vs sham: 24.6% less ($p = 0.245$) | F3 cathodal vs sham: 32% less ($p = 0.258$). ES = 0.53 | [51] |
| | | | F3 anodal vs sham: 42% less ($p = 0.093$) | F3 anodal vs sham: 10.4% less ($p = 0.675$) | F3 anodal vs sham: 7.6% more ($p = 0.771$). ES = -0.085 | |
| | | | F3 cathodal vs anodal: 1.7% less ($p = 0.879$) | F3 cathodal vs anodal: 15.9% less ($p = 0.421$) | F3 cathodal vs anodal: 36.6% less ($p = 0.445$). ES = 0.5 | |
| Glaser *et al.* | 2016 | 27 | – | – | 23.6% less ($p < 0.001$). ES = 0.3 | [56] |
| Khedr *et al.* | 2017 | 48 | 5% less ($p = 0.411$) | – | 26% less ($p = 0.0002$). ES = 0.646 | [52] |
| Ribeiro *et al.* | 2017 | 40 | Less pain ($p < 0.001$) | Less pain ($p < 0.001$) | 73.25% less ($p < 0.001$). ES = 0.692 | [57] |

Table shows pain scores measured by VAS and by PCA.
ES: Effect size; F3: Left dorsolateral prefrontal cortex according to the 10–20 EEG system; PCA: Patient-controlled analgesia; VAS: Visual analog scale.

Regarding the number of tDCS sessions, a single one was applied in two studies [51,54] and two or more tDCS sessions in five other studies [52,53,55–57]. Six studies [51–56] performed tDCS immediately after surgery and only one study [57] applied tDCS prior to the surgery. The duration of stimulation was the same; however, current intensity differed among studies. Six out of seven studies [52–57] applied 2 mA stimulation and one [51] applied 1 mA stimulation.

Five out of seven papers [51,52,54–56] reported adverse events and none of them were considered serious (Appendix 3). Tingling, itching, mild stinging and burning sensations were the most common adverse events. Dubois *et al.* [51] also described a visual flash sensation experienced by one of the subjects (out of 20 in the cathodal stimulation group) at the start of the stimulation.

In terms of the results from these clinical trials, the most clear and significant results came from patient-controlled analgesia (PCA). This outcome measures the usage of self-administered opioids. In five studies [52–54,56,57], a reduction of the PCA was observed varying from 22 to 73.25%, and the differences were statistically significant. In Dubois *et al.* [51], however, no statistically significant differences were observed in relation to this parameter. And in Borckardt *et al.* [55], the group in which the anode was positioned over F3 presented a reduction of 24% in the consumption of opioids, while the group with the anode positioned over motor cortex (C1 or C2) showed an increase in consumption by 27% as compared with the sham, both differences with $p < 0.05$. Given the limited data, it is difficult to state that M1 stimulation in this study resulted in increased opioid use compared with other studies. Authors speculated that the observed difference in the first scenario is due to the fact that the cathodal stimulation of the right DLPFC might have limited the pain relief role of the M1 anodal stimulation; in the second scenario, authors hypothesized that the cathodal stimulation of the sensory cortex might have enhanced the analgesic effects of the left DLPFC anodal stimulation. Finally, visual analog scale results were only significant in one study [57] that measured the tDCS analgesic effects considering pain scores at rest and during walking for the first 48 postoperative hours and throughout the 7-day postoperative period. Mainly, active tDCS, compared with sham stimulation, resulted in less pain in both conditions in all time points considered (Table 2).

## Results 'tDCS to treat opioid dependence'

The search for studies assessing the impact of tDCS on opioid dependence and misuse retrieved only one new paper [58]. The randomized, single-blinded and sham-controlled study was conducted in China and included

individuals who experienced addiction for >3 continuous years and were abstinent from heroine for at least 1.5–2 years. Twenty male subjects with a mean age of 39.8 (standard deviation [SD] = 1.8) and history of 5–25 years of heroin dependence (mean = 16.9 years, SD = 1.1) were randomly assigned to receive active (cathode over T3 and T4, and anode over O2 and O1) or sham stimulation. A single stimulation session lasting 20 min with a current intensity of 1.5 mA was applied. As the primary outcome, investigators exposed the subjects to a real video of heroin use and asked them to fill out the craving questionnaire before and after tDCS. The group that received active stimulation showed a decrease of 36.7% on the craving score (p = 0.003), while no difference between pre and post tDCS stimulation was observed in the sham group.

## Discussion

This review aimed to identify the level of evidence about the effect of tDCS in preventing and treating postsurgical pain and opioid dependence. We performed two different searches and eight papers were retrieved.

The studies selected appear quite different in regards to the stimulation procedure, suggesting that there are different strategies for the treatment of pain and prevention of opioid dependence using noninvasive stimulation. We observed that all studies included in this review performed 20 min of tDCS stimulation at a current intensity of 1–2 mA (in line with the safety standards) [59], and positioned electrodes following the 10–20 EEG system or its variations. However, the current density, the montage and the number of intervals between sessions were not standardized across studies.

All eight studies included in the present review targeted mainly two brain areas, the M1 and the DLPFC. As aforementioned, these two regions play a crucial role in pain and opioid addiction. While M1 is believed to modulate the somatosensory system and thus reduce overactivation in these circuits, the DLPFC (also part of the inhibitory control system) is believed to modulate the affective aspects of pain [60–63]. The DLPFC is also important for both pain control [62,64,65] and reward responses modulation, representing a crucial target when dealing with craving [66]. The literature has supported the role of mesolimbic and mesocortical dopamine pathways in reward circuit, especially the tegmental area and the nucleus accumbens [67,68] as well as the amygdala and the hippocampus, involved in generating conditioned responses and underlying emotional memories and the orbitofrontal cortex, crucial for computing the value of stimuli and driving motivation [68,69]. Overall, the studies analyzed here support the idea that tDCS strengthens top-down regulation processes in both pain modulation and opioid dependence [55,56,58].

Regarding pain modulation, stimulation of the DLPFC could affect the limbic structures, resulting in a better control of emotional components of pain [31,32,70,71]. TDCS over M1 could have indirect effects on the thalamus, modulating pain-related areas and nociceptive pathways [34,72,73]. This pain control might in turn contribute to the reduction of opioid consumption. The potential postoperative pain reduction role of the neuro stimulation techniques has been also investigated with repetitive transcranial magnetic stimulation. In two studies, repetitive transcranial magnetic stimulation was applied over the left DLPFC in subjects that underwent to gastric bypass surgery. Results are similar and showed reduction in consumption of morphine of 36 [74] and 40% [75], respectively. Regarding opioid dependence, tDCS over the DLPFC could affect dopaminergic pathways, downregulating the reward system responses [58,76–79]. Alternately, tDCS stimulation of the DLPFC could strengthen executive functions, such as decision making and response inhibition [29,80,81]. Interestingly, these processes are reported also by studies interested in investigating the tDCS effects on food craving [82]. Indeed, the same neural system seems to be active for both natural rewards (e.g., food) and addictive drugs [69,83].

Regarding the localization of the stimulation, the role of M1 stimulation was shown by Khedr *et al.* [52]. In this study, an extracephalic montage with the anode over M1 resulted in similar findings to those achieved by Borckardt and collaborators in 2013 [53], counteracting the possibility that targeting both DLPFC and M1 could reduce the M1 stimulation effectiveness in reducing pain. However, Borckardt *et al.* found later in 2017 [55] that anodal tDCS over M1 caused an increased consumption of hydromorphone in contrast to what the same research group observed previously [53]. Beyond possible antagonistic effects of DLPFC downregulation action on M1 stimulation, authors did not exclude experimenter effects linked to the single-blind design they used in the 2013 trial [53]. This suggests the need for future studies of more rigorous methodology (e.g., double-blind design) to improve results' reliability. To this regard, Dubois *et al.* [51], considering both PCA morphine consumption and pain scores, did not observe statistically different effects between the three stimulation conditions (i.e., anodal, cathodal or sham) when applied over the left DLPFC. The relatively underpowered number of patients for each stimulation group (20 patients for anodal stimulation; 20 patients for cathodal stimulation; 19 patients for sham stimulation) could at least in part

underlie the findings, leading to a type II error. Moreover, this trial is the only one among those retrieved that used a current intensity of 1 mA, which may explain, in part, the lack of significant results. Prospectively, standardizing stimulation parameters among studies could help to compare different trials effectively.

A final important consideration here is the large variation of the location of the other return electrode. For instance, for M1 stimulation, there were four different montages (considering the return electrode: supraorbital [SO], somatosensory, DLPFC and extracephalic). It should be noted that the return electrode is critical for the induced current and thus the potential clinical effects. In a previous pain-modeling study, we showed that changing the return electrode resulted in no significant results and current was significantly displaced [84].

## tDCS to prevent & treat postoperative pain

### *Surgical procedures*

To assess the possible analgesic effects of tDCS in the postoperative population, we included all studies conducted in a surgical setting without filtering the results based on surgical technique and procedures. This resulted in a variety of interventions (i.e., endoscopic retrograde cholangiopancreatography [54], total knee arthroplasty [52,53,55], lumbar spine surgeries – fusion procedures, decompression, herniated disc repair, laminectomy and hardware revision [51,56] – and hallux valgus surgery [57]). It is possible to infer that the surgical interventions were not standardized for all the subjects, which might be considered a confounding factor, since different surgical procedures involve distinct organs and tissues which create a variety of patterns of nociceptor sensitization and differences in the quality, location and intensity of postoperative pain. Hence, standardizing surgical procedures in these kinds of studies seems to be a crucial factor since it improves the reliability of the experiments and helps the interpretation of the observed tDCS effects. However, it may be an important limitation for subjects' inclusion and poorly realistic with surgical practice.

### *Components of pain*

The onset of pain is an important factor to consider when tDCS is performed. Even though acute and chronic pain involves common pathways, long-term experience of pain may induce changes in brain processes that would not be provoked by acute pain [85]. Acute pain involves mainly the somatosensory cortex during injury and inflammatory processes as a transient adaptive response [86], while chronic pain induces plastic changes in both the limbic system and cortical structures such as the somatosensory and prefrontal cortex [87]. Studies performed in populations that experience chronic pain show cortical reorganization as a possible factor to pain perpetuation [86,87]. Therefore, pain chronicity could affect the tDCS modulatory effects. The majority of studies (five out of seven) found in this review did not describe the exact onset of pain, even though it is reasonable to assume that most of the patients were facing chronic pain, which constitutes an indication to an elective surgical procedure. The effects of tDCS on chronic pain have already been extensively described in the literature in various pathologies [88,89]; however, future studies should control for pain chronicity to better clarify the tDCS analgesic effects.

Moreover, not only the onset of pain but also the emotional components of pain seem to be crucial. Among the studies retrieved by this review, only the one of Ribeiro *et al.* [57] assessed the pain-related catastrophic thinking using the Brazilian Portuguese Catastrophizing Scale, showing a medium effect size of 0.37 following the intervention. This suggests the need for future studies to control for the catastrophic behavior, which represents a stable and independent from physical impairment [90] feature of several pain syndromes such as rheumatoid arthritis, fibromyalgia and low back pain [91–95]. Particularly, the catastrophizing thinking, being the tendency to magnify the threat value of pain, to feel helpless and to be unable to prevent or inhibit pain-related thoughts, could negatively affect how subjects perceive pain and increase pain-related disability, emotional distress as well as avoidance behavior [96–99]. Previous evidence in patients with fibromyalgia showed a relationship between catastrophizing and the activity of brain areas involved in the anticipation of pain, attention to pain and pain-related emotional processing, mainly the medial frontal cortex, the DLPFC, the anterior cingulated cortex and amygdala [100]. Since these areas underlie top-down cognitive and emotional modulation of pain [101], abnormalities in descending modulatory systems in patients with chronic pain could explain these results [102,103] and those related to hyperexcitability of pain pathways [85]. Therefore, tDCS could effectively be applied to improve the disinhibited state of cortical neural circuits, resulting in a better control of both pain [31,57] and pain-related emotions [104].

### *Follow-up time*

The short follow-up time adopted by the seven papers does not allow us to infer about perpetuation effects of stimulation and triggers the possibility of higher demand of analgesics at discharge. Also, none of the studies discussed if the statistical differences observed in pain scales after tDCS could be translated to a clinical meaningful difference.

## tDCS to treat opioid dependence

Wang *et al.* [58] provided promising results, showing that active tDCS significantly reduced craving scores when heroin-addicted subjects were exposed to videos of both heroin injection and inhalation. However, some limits in this study must be discussed. First, subjects' heroin use history. Although authors controlled for the abstinence period, they did not consider the individual differences regarding heroin use history length. Indeed, we can speculate that few years of heroin addiction correspond to low level of chronicity, representing a protective factor toward structural and functional alterations of brain areas involved in drug addiction [105–107]. This, in turn, could influence the tDCS effects. Indeed, a growing literature is reporting a certain individual variability of tDCS effects, suggesting the need of tailoring personalized stimulation protocols [108–111]. Second, another possible confounder factor is related to difference in pretreatment craving scores between the two experimental groups. The fact that the tDCS group had a higher pretreatment craving score than the sham group, even though the difference was not statistically significant, could underlie a greater sensitivity of subjects in tDCS group to stimulation's effects and explain in part the results. Although the study is a Phase II trial and therefore does not aim at external validity, the extremely homogeneous characteristics of the sample (e.g., only male subjects, same period of abstinence) do not allow for the generalizability of the results in other populations. Future studies need to test tDCS effects on opioid consumption considering larger samples and both genders. Moreover, even though presenting real video or images of craving-induced stimuli to explore tDCS effects on craving is common [82,112,113], it is important to consider whether this could trigger an after-study increase in exposure to drugs. Exposing subjects with an addiction history to addiction-related stimuli could result in an increased risk of relapse [69]. Hence, alternative stimuli should be taken into account to ensure safer experimental settings.

## Limitations

The main limitation in this review is the number of articles and the important heterogeneity among them precluding drawing more firm conclusions regarding the use of tDCS to prevent and treat opioid dependence in postsurgical opioid dependence. However, this is an important emerging research area that can have a significant impact in public health, given the opioid epidemic and given the lack of cost-effective alternatives. In addition, most of the studies using different strategies show significant effects; thus it is important to discuss these initial studies as to help researchers designing future trials in this topic.

## Conclusion & future perspective

Despite the limited number of studies assessing tDCS effects in controlling postsurgical pain and opioid dependence, the results of this review showed encouraging directions. However, some considerations should be taken into account for future clinical trials testing the effects of tDCS in the field of surgical pain and opioid dependence. First, clinical research focused on pain management is difficult to carry out: high drop-out rates and several ethical concerns are typical of these kinds of studies. The growing amount of studies using home-based protocols [114–117] may overcome this limitation; especially given the importance to increase the number of sessions to enhance their clinical effects [84]. Furthermore, individuals suffering from pain are extremely vulnerable to placebo effect [118,119]. Thus, a run-in-phase approach and more rigorous methodologies, including double-blind designs, should be considered. Longer follow-ups are also needed to evaluate the long-term effects of stimulation in postsurgical pain and opioid dependence. Finally, it is important to find out which strategy would be most effective, but also certainly preventive strategies are worthwhile to be considered with priority. We recently showed that tDCS can indeed prevent stress-induced pain in animals [120]. Based on this review, even if the available data are still limited, tDCS seems to represent a safe and inexpensive tool to prevent and treat postsurgical pain and analgesic overuse.

## Executive summary

- Nowadays, opioid dependence represents a major problem, with high mortality rates and costs for health systems.
- Opioid therapies are mainly prescribed to treat postoperative pain.
- The burdens of traditional pharmacological interventions to deal with opioid dependence have led to the search of alternative treatments.
- Transcranial direct current stimulation, being safe, simple, inexpensive and a well-tolerated neuromodulation technique, has demonstrated positive effects on both chronic pain and opioid addiction.
- The eight studies retrieved by this review showed that M1 and the dorsolateral prefrontal cortex might be preferential stimulation targets.
- Despite the limitations, our review provides promising data regarding the role of transcranial direct current stimulation in enhancing top-down regulation processes that interfere with pain-related areas and the reward system.

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