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Review Article

Noninvasive Brain Stimulation for Cancer Pain Management in Nonbrain Malignancy: A Meta-Analysis

Yung-Jiun Chien,[1,2] **Chun-Yu Chang**,[2,3] **Meng-Yu Wu**,[2,4] **Yung-Chen Chien**,[5] **Hsin-Chi Wu**,[1,2] **and Yi-Shiung Horng**[1,2]

[1]*Department of Physical Medicine and Rehabilitation, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City 231, Taiwan*
[2]*School of Medicine, Tzu Chi University, Hualien 970, Taiwan*
[3]*Department of Anesthesiology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taipei City 231, Taiwan*
[4]*Department of Emergency Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City 231, Taiwan*
[5]*Department of Obstetrics and Gynecology, Taipei Medical University Hospital, Taipei City 110, Taiwan*

Correspondence should be addressed to Yi-Shiung Horng; yshorng2015@gmail.com

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Purpose. Noninvasive brain stimulation (NIBS) has been reported to have analgesic effects on fibromyalgia and chronic neuropathic pain; however, its effects on cancer pain have yet to be determined. The present study aimed to evaluate the effects of NIBS on patients with pain secondary to nonbrain malignancy. *Methods*. Electronic databases including PubMed, Embase, Cochrane Library, and Web of Science were searched from inception through June 5th, 2022. Parallel, randomized, placebo-controlled studies were included that enrolled adult patients with cancer pain, except for that caused by brain tumors, compared NIBS with placebo stimulation, and reported sufficient data for performing meta-analysis. *Results*. Four parallel, randomized, sham-controlled studies were included: two of repetitive transcranial magnetic stimulation (rTMS), one of transcranial direct current stimulation (tDCS), and one of cranial electrical stimulation (CES). rTMS significantly improved pain in the subgroup analysis (standardized mean difference (SMD): −1.148, 95% confidence interval (CI): −1.660 to −0.637, ($p < 0.001$)), while NIBS was not benefited in reducing pain intensity (SMD: −0.632, 95% CI: −1.356 to 0.092, $p = 0.087$). Also, NIBS significantly improved depressive symptoms (SMD: −0.665, 95% CI: −1.178 to −0.153, $p = 0.011$), especially in the form of rTMS (SMD: −0.875, 95% CI: −1.356 to −0.395, $p < 0.001$) and tDCS (SMD: −1.082, 95% CI: −1.746 to −0.418, $p = 0.001$). *Conclusion*. rTMS significantly improved pain secondary to nonbrain malignancy apart from other forms of NIBS without major adverse events.

1. Introduction

Cancer patients frequently experience pain, and almost 40% of cancer patients experience moderate to severe pain that significantly impacts their physical function, psychological status, and activities of daily living [1, 2]. The heterogeneity of cancer pain can be broadly characterized by direct visceral damage from primary or metastatic tumors or by indirect tissue or nerve damage from cancer-related treatments or comorbidities [3, 4]. Cancer cells cause pain by activating C- and A-delta fibers via endothelin-1 and indirectly upregulating substance P by binding nerve growth factors to the tyrosine kinase receptor [5–7]. The afferent nociceptive signals are transmitted from the dorsal horn of the spinal cord to the thalamus through the ascending spinothalamic pathway; relayed to the amygdala, insula, and anterior cingulate gyrus; and regulated via the primary sensory cortex, prefrontal cortex, and other cortical and subcortical regions [8]. As the duration and extent of cancer pain increase, the overt sensitized nociceptive receptors in tissues amplify the nociceptive

input, causing central sensitization [9]. Central sensitization changes cortical activity and escalates pain severity, leading to a vicious cycle of uncontrolled pain [10].

Although the adequacy of analgesic medications has gradually improved over time with the recommendation of the WHO three-step ladder approach, approximately 25% of patients with cancer pain remain undertreated [11, 12]. In addition to the complicated and multifactorial mechanisms of cancer pain, the challenges involve both patients' and healthcare professionals' concerns about opioid addiction and the side effects of long-term analgesic treatment [13]. Non-pharmaceutical therapies, particularly neuromodulation techniques that modulate central or peripheral nervous systems by energy stimuli, have been extensively studied as adjunctive management approaches to cancer pain [14, 15].

Noninvasive brain stimulation (NIBS) is a neuromodulation technique that alters the excitability of the neural circuit of the brain with electric or magnetic stimulation without invasive procedures [16]. Some of the most common NIBS approaches include transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and cranial electrical stimulation (CES) [17]. tDCS produces a constant, low-amplitude direct electric current transmitted from the target and reference electrodes on the scalp, causing excitatory or inhibitory effects with anodal or cathodal stimulation [18]. rTMS produces repeated magnetic pulses with either excitatory high-frequency stimulation ($\geq$5 Hz) or inhibitory low-frequency stimulation ($\leq$1 Hz) via a magnetic coil [19]. CES delivers a low-intensity electrical current at 50 microamperes (μA) to 4 milliamperes (mA) with a pair of electrodes attached to the bilateral earlobes [20]. rTMS and tDCS regulate the pain signaling pathway by inducing excitatory glutamatergic neurotransmitters or inhibitory γ-aminobutyric acid (GABA) neurotransmitters in pain perception areas, such as the thalamus and prefrontal cortex, leading to activation of the descending pain inhibitory system through the periaqueductal gray, rostroventromedial medulla, and dorsal horn of the spinal cord pathway [19, 21, 22]. CES suppresses the thalamocortical tract by interacting with the cholinergic activity in locus coeruleus and adrenergic neurotransmitters in laterodorsal tegmental nucleus of the brainstem [23]. In addition, NIBS can also induce endogenous opioids, serotonin, β-endorphin, or brain-derived neurotrophic factors, which further suppress pain transmission [23–25]. Studies have demonstrated that NIBS approaches, including tDCS, rTMS, and CES, have significant chronic pain-relieving effects [26–28]. Invasive brain stimulation, such as deep brain stimulation, has been reported to have pain-relieving effects in cancer patients [29, 30]. In contrast, the effects of NIBS on cancer pain have yet to be determined. The present study aimed to evaluate the analgesic effects of NIBS in patients with cancer pain secondary to nonbrain malignancy.

2. Methods

2.1. Study Design. This was a systematic review and meta-analysis of randomized controlled trials (RCTs). The primary outcome was the evaluation of the analgesic effects of NIBS on cancer patients without brain malignancy, assessed by pain intensity using the visual analogue scale (VAS), numeric pain rating scale (NPRS), brief pain inventory (BPI), and other formal verified scales. The secondary outcome was the assessment of the effects of the NIBS intervention on depression and anxiety using the Hamilton depression/anxiety rating scale (HAM-D/HAM-A), hospital anxiety and depression scale (HADS), and other formal verified scales. The present study was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42022339131) and adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [31].

2.2. Search Strategy. Two authors (Y. J. Chien and C. Y. Chang) searched the PubMed, Embase, Cochrane Library, and Web of Science databases from inception through June 5th, 2022. The search strategy was constructed with medical subject headings (MeSH) and keywords with search terms, such as "brain stimulation", "cranial stimulation", "noninvasive brain stimulation", "neoplasms", "tumor", "malignancy", "cancer", and "cancer pain". The complete search strategy is provided in Supplementary Table S1. Search terms were entered with the Boolean operators "OR" and "AND" to combine or intersect different concepts, respectively. First, the titles, abstracts, and keywords of the identified studies were screened, and then, the potential eligible studies were subjected to a full-text review.

2.3. Eligibility Criteria. The selection criteria for study inclusion followed the population, intervention, comparison, outcome (PICO) framework and were defined as follows: (1) the study involved adults with cancer pain either directly caused by a tumor or indirectly caused by cancer-related treatment; (2) the study compared noninvasive brain stimulation with sham stimulation; and (3) the study reported relevant outcomes and sufficient information to calculate the effect estimates in meta-analysis. Patients with cancer pain secondary to brain malignancy are excluded to prevent obscuring the possible interaction between brain stimulation and malignancy. Additionally, brain stimulation with diagnostic or preoperative navigated application was excluded. Finally, studies that were not randomized parallel studies were excluded. A third author (M. Y. Wu) made the final decision if there was any disagreement about the study selection.

2.4. Risk of Bias Assessment. The methodological quality of each study was assessed independently by two authors (Y. J. Chien and C. Y. Chang) with the revised Cochrane Risk of Bias Tool 2 (ROB2) [23]. ROB2 is a structural assessment in evaluating different aspects of bias in randomized controlled trials, including trial design, randomization, and blinding. Subsequently, a final judgment with "low," "some concerns" or "high" risk of bias was decided by an algorithm based on the aforementioned evaluation. The detailed risks of bias assessment are listed in Supplementary Figure S2. Disagreements were solved by discussion with a third reviewer (M. Y. Wu).

2.5. Data Extraction. Data from each eligible study were extracted by one author (Y. J. Chien) and confirmed by another author (C. Y. Chang). The required information included the author's name, publication year, number of patients, cancer type, NIBS targeted location, intervention regimen, concurrent analgesic medications, and adverse effects. The data of effect estimates of NIBS on the outcomes of interest were extracted on the final day of the intervention regimen.

2.6. Statistical Analysis. The effects of NIBS reported with continuous outcome variables were evaluated by comparing the mean difference (MD) and standard deviation (SD) before and after treatment in the intervention group versus those in the sham stimulation group. The subgroup was identified with different NIBS techniques prior to the meta-analysis. The meta-analysis was performed with random-effect models due to the assumption that the studies differed regarding cancer type, mean patient age, and country. The inverse-variance method was used to combine the data from individual studies in the meta-analysis. Statistical heterogeneity was calculated by Cochran's Q and quantified by I^2. The heterogeneity was classified as low, moderate, and high with an I^2 of <50%, 50%–74%, and ≥75%, respectively [32]. The influence analysis was carried out as a sensitivity analysis by excluding one study at a time and recalculating the results from each subset of studies. The statistical analyses were carried out using R software version 4.1.3 with "dmetar", "meta", and "metafor" packages. A p value <0.05 was considered statistically significant.

3. Results

3.1. Study Identification and Selection. A total of 6051 studies were identified from the PubMed ($n = 2572$), EMBASE ($n = 2690$), Cochrane Library ($n = 190$), and Web of Science ($n = 599$) databases. After removing 1223 duplicates, the remaining studies were screened for eligibility. A total of 4750 records were excluded due to irrelevant topics determined by screening titles and abstracts. Therefore, 69 studies were assessed with a full-text review. Sixty-five studies were excluded as they were ongoing trials, irrelevant, non-RCT design or had inadequate data relevant to the outcomes of interest. Finally, 4 studies involving 280 patients were included. The detailed PRISMA flow diagram is presented in Figure 1.

3.2. Study Characteristics and Risk of Bias Assessment. The characteristics and outcomes of interest at baseline of the four included studies are listed in Tables 1 and 2. All studies were double-blind, parallel, sham-controlled RCTs with no baseline demographic differences. The included studies enrolled a total of 269 patients with pain secondary to malignancy including hepatocellular carcinoma (HCC) [33], breast cancer [35], nonsmall cell lung cancer (NSCLC) [36], or mixed-origin cancers [34]. Most of the studies reported chronic (at least 2 months) and uncontrolled pain secondary to the cancer itself or to cancer-related treatments, including surgery, chemotherapy, or radiotherapy [33, 35, 36].

In Ibrahim et al.'s study, 40 patients with HCC had uncontrolled abdominal pain with VAS pain scores ranging from 6.5 to 6.85 [33]. The patients received tDCS at the primary motor cortex (M1) cortex contralateral to the most painful side with stimulation at 2 mA for 30 minutes for a total of 10 sessions. The pain score was evaluated at the 1st, 5th, and 10th sessions and at follow-up one month later. In Khedr et al.'s study, a total of 32 patients with pain secondary to malignancy received rTMS at the contralateral M1 cortex with 2000 pulses of 20 Hz stimulation for 10 consecutive days [34]. The initial VAS pain score ranged from 6.1 to 6.3 and was reevaluated at the 1st, 5th, and 10th sessions and at follow-up 15 days and 1 month later. Lyon et al.'s study evaluated 158 patients with pain secondary to breast cancer [35]. The baseline pain score was rated with the BPI at 1.24 to 1.45 and reevaluated twice during CES treatment of 1 hour stimulation per day for 2 weeks. In Tang et al.'s study, 39 patients with NSCLC had intractable pain even with the use of morphine or oxycodone [36]. The patients received rTMS for 3 weeks targeting the left dorsolateral prefrontal cortex (DLPFC) with 1500 pulses of 10 Hz stimulation for 3 weeks. The initial pain score was evaluated by NPRS at 6.4 to 6.5 and reevaluated at the 3rd, 5th, 10^{th}, and 15th sessions. Sham stimulation included turning off the device without the participants' awareness [33], angling the setup away from the targeted brain location [34, 36] or using sham devices [35].

The data regarding the outcomes of interest were extracted from individual studies and are presented in Table 2. All of the included studies had low risks of bias despite concerns about randomization concealment and missing outcomes from participants who withdrew from the study. Notably, patients predominantly withdrew for disease-related reasons [33, 34, 36], and patient adherence was high ranging from 83.3% to 100% [33, 35]. The details of the risks of bias assessment are listed in Supplementary Figure S2.

3.3. Outcomes

3.3.1. Pain Intensity. The forest plots of pain intensity and the subgroups from different NIBS approaches are presented in Figure 2. The improvement in pain intensity was not significant in response to NIBS compared to that in response to sham stimulation (SMD: −0.632, 95% CI: −1.356 to 0.092; $P = 0.087$; $I^2 = 87.9\%$). In the subgroup of rTMS, the effect of pain intensity was significant (SMD: −1.148, 95% CI: −1.660 to −0.637; $P < 0.001$).

3.3.2. Depression and Anxiety. The forest plot for depressive symptoms is presented in Figure 3. NIBS significantly reduced depressive symptoms with substantial heterogeneity (SMD: −0.665, 95% CI: −1.178 to −0.153; $P = 0.011$; $I^2 = 75.2\%$). While the subgroups of both rTMS (SMD: −0.875, 95% CI: −1.356 to −0.395; $P < 0.001$) and tDCS (SMD: −1.082, 95% CI: −1.746 to −0.418; $P = 0.001$) significantly reduced depressive symptoms, CES did not.

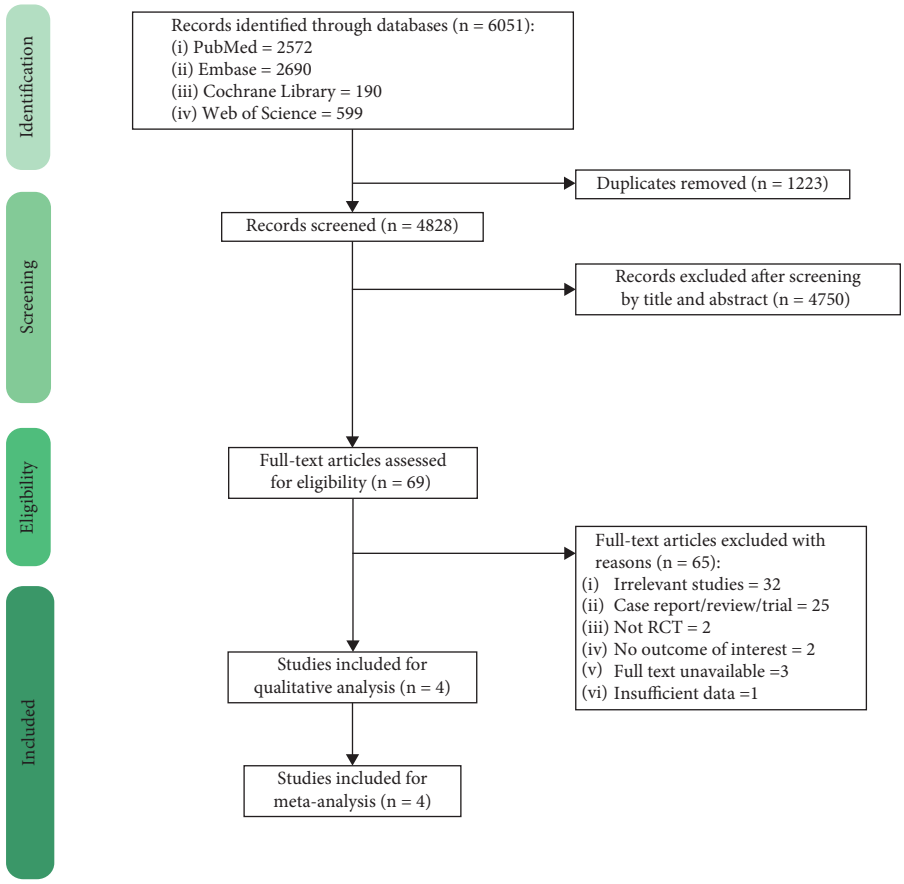

Figure 1: PRISMA flow diagram.

The forest plot for anxiety is presented in Figure 4. NIBS neither CES nor rTMS significantly improved anxiety (SMD: −0.396, 95% CI: −1.293 to −0.501; $P = 0.387$).

3.3.3. Influence Analysis. The influence analysis is presented in Supplementary Figures S3 to S5. In the outcomes of pain intensity, depression, and anxiety, the influence analysis with the "leave-one-out" method revealed that the pooled point estimates were within the 95% CI of the overall pooled effect. Therefore, neither of the studies had a significantly large influence that distorted the overall effect.

3.3.4. Publication Bias. Despite the predetermined assessment for publication bias, a funnel plot was not indicated due to the limited number of included studies.

4. Discussion

The present study showed that rTMS significantly reduced pain intensity in nonbrain malignancy patients, while other forms of NIBS had limited effects. In addition, NIBS approaches, particularly tDCS and rTMS, significantly reduced depressive symptoms in cancer patients. However, NIBS was ineffective for anxiety.

Approximately 38% of the patients with chronic and advanced cancer pain had neglected signs of central sensitization with prevalence increasing with pain intensity [37]. Central sensitization is characterized by hyperresponsiveness of the subthreshold nociceptive input to overt sensitized receptors which is associated with long-term potentiation (LTP), a molecular process of enhancing synaptic plasticity [38]. Nociceptive stimulation activates glutamate NMDA receptors, leading to calcium influx, and triggering the calcium-dependent intracellular pathway to induce LTP, notably the calcium/calmodulin-dependent protein kinase II (CaMKII) pathway [9, 39]. LTP was shown to be associated with the analgesic mechanisms in NIBS [40]. It has been reported that rTMS reduces central sensitization by 70% according to the central sensitization inventory score [41]. In summary, the analgesic effects of NIBS act through the sensory network of the cortex, limbic system, thalamus, and hypothalamus and through the induction of LTP to reduce central sensitization, decreasing pain intensity from a "top-down" approach [42–44].

The application of NIBS has been extensively studied in various chronic pain conditions. Guidelines recommend high-frequency rTMS for the M1 contralateral to the side of pain for treating neuropathic pain (level A) and high-frequency rTMS for the left M1/DLPFC or anodal tDCS for the left M1 in decreasing pain in fibromyalgia (level B) [45, 46]. A previous review summarized the beneficial effects of rTMS and tDCS, but not CES for chronic pain [47]. Recently, case studies have shown promising results in refractory cancer pain management with decreasing pain scores with rTMS, tDCS, and CES [48–50]. Our

Table 1: Study characteristics.

Studies	Study design	Cancer type	Concurrent analgesic treatment	Intervention type/location	Outcome measurement timeline	Sample size Intervention (M : F)/ control (M : F)	Mean age† Intervention/ control	Regimen Intervention	Regimen Control	Adverse events
Ibrahim et al. [33]	Double-blind, sham-controlled RCT	HCC	Tramadol 50 mg BID	tDCS/ contralateral M1	1st, 5th, 10th sessions, and one month later	20 (14 : 6)/20 (13 : 7)	58.9 (5.6)/ 56.85 (9.16)	2 mA for 30 minutes per session, 10 sessions in 2 weeks	Sham stimulation	Burning sensation, skin redness
Khedr et al. [34]	Double-blind, sham-controlled RCT	Mixed	Tramadol 100 mg BID Pregabalin 75 mg BID Gabapentin 400 mg BID Amitriptyline 25 mg BID	rTMS/ contralateral M1	1st, 5th, 10th sessions, and 15 days, one month later	17 (1 : 16)/15 (2 : 15)§	47.0 (9.2)/48.0 (9.7)	2000 pulses of 20 Hz of rTMS, 80% RMT for 10 consecutive days	Sham stimulation	Nil
Lyon et al. [35]	Double-blind, sham-controlled RCT	Breast cancer	Long-acting opioids, NSAIDs‡	CES	1st week, 2nd week	81 (0 : 81)/77 (0 : 77)	51.04(1.21)/ 51.91 (0.97)	1 hour daily for 2 weeks	Sham device	Seizure
Tang et al. [36]	Double-blind, sham-controlled RCT	NSCLC	Morphine or oxycodone	rTMS/left DLPFC	3rd, 5th, 10th, 15th sessions	20 (12 : 8)/19 (10 : 9)	58.5(8.9)/59.6 (7.7)	1500 pulses of 10 Hz of rTMS, 80% RMT once a day, 5 days per week for 3 weeks	Sham stimulation	Scalp numbness, facial twitching

†Mean age is presented as mean (standard deviation). ‡21.47% of participants receiving long-acting opioids, and 18.40% of participants receiving NSAIDS without specified regimen in the study. §Two participants in sham group dropped out due to disease complications without specifying gender. *Note.* M : F: male : female; RCT: randomized control trial; HCC: hepatocellular carcinoma; NSCLC: nonsmall cell lung cancer; NSAIDs: nonsteroidal anti-inflammatory drug; BID: twice per day; M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; tDCS: transcranial direct current stimulation; rTMS: repetitive transcranial magnetic stimulation; CES: cranial electrical stimulation; RMT: resting motor threshold.

Table 2: Measurement of pain intensity, depression, and anxiety.

Studies	Scale	Intervention		Placebo	
		Pretreatment Mean (SD)	Posttreatment Mean (SD)	Pretreatment Mean (SD)	Posttreatment Mean (SD)
Pain intensity					
Ibrahim et al. [33]	VAS	6.50 (1.88)	3.50 (2.01)	6.85 (1.76)	5.37 (2.80)
Khedr et al. [34]	VAS	6.30 (0.50)	3.87 (0.99)	6.10 (0.60)	5.11 (1.00)
Lyon et al. [35]	BPI	1.24 (2.05)	1.14 (1.65)	1.45 (1.98)	1.32 (1.80)
Tang et al. [36]	NPRS	6.50 (1.70)	3.80 (1.40)	6.40 (1.60)	4.90 (1.20)
Depression					
Ibrahim et al. [33]	HAM-D	17.00 (5.30)	10.10 (5.49)	16.85 (3.22)	14.95 (3.54)
Khedr et al. [34]	HAM-D	13.30 (1.90)	10.19 (2.02)	13.5 (1.50)	12.17 (1.64)
Lyon et al. [35]	HADS	3.03 (2.48)	4.47 (3.36)	3.06 (2.78)	4.63 (3.67)
Tang et al. [36]	HAM-D	14.10 (5.90)	9.90 (3.60)	14.30 (5.40)	13.20 (4.20)
Anxiety					
Lyon et al. [35]	HADS	7.09 (4.09)	4.07 (3.51)	7.59 (4.13)	4.51 (4.04)
Tang et al. [36]	HAM-A	13.30 (6.50)	9.10 (3.90)	13.60 (5.70)	13.20 (4.50)

Note. VAS: visual analogue scale; NPRS: numeric pain rating scale; BPI: brief pain inventory; HAM-D: Hamilton depression rating scale; HADS: hospital anxiety and depression scale; HAM-A: Hamilton anxiety rating scale.

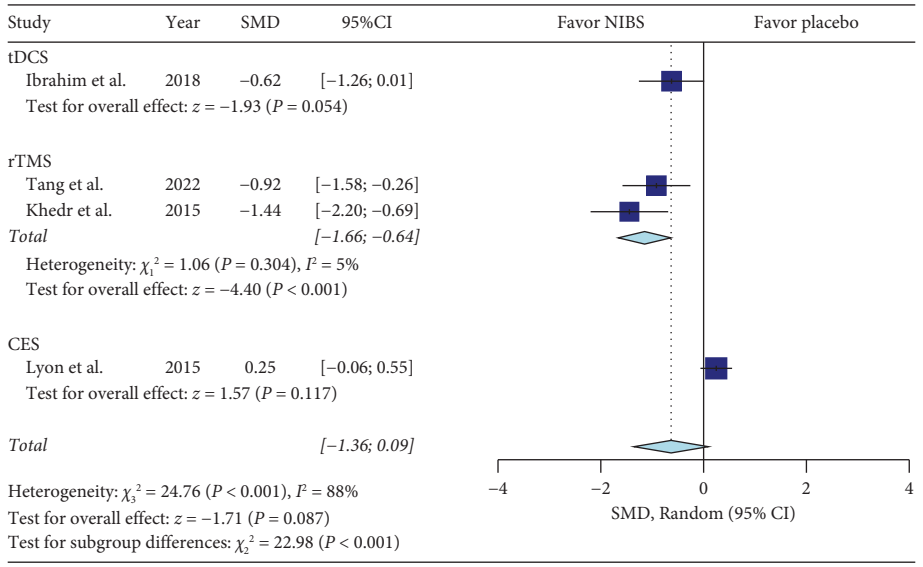

Figure 2: Forest plot of pain intensity.

meta-analysis demonstrates the effectiveness of high-frequency rTMS but not tDCS and CES for cancer pain. The results of this study are comparable to those of a previous network meta-analysis that showed that the pain score of the rTMS group was significantly lower than that of the control group (SMD: −0.92, 95% CI: −1.56 to −0.28; $P = 0.01$), while that of the tDCS group was not (SMD: −0.70, 95% CI: −1.45 to 0.04; $P = 0.06$). Moreover, a recent head-to-head randomized trial showed that rTMS was superior to tDCS in improving neuropathic pain [51, 52]. The advantage of rTMS compared to tDCS and CES results from a higher intensity with a more focused electrical field [53]. The electric field produced in the brain tissue is proportional to the current intensity generated by the NIBS device [54]. rTMS generates a high electric current at several thousand amperes, while most studies apply tDCS at 1.0 to 2.0 mA [54, 55]. The simulated electric field of TMS is approximately 200 times stronger than that of tDCS [56].

We also demonstrated the benefits of treating depressive symptoms with NIBS, particularly rTMS and tDCS. Although rTMS of the left DLPFC was demonstrated level A evidence for treating depression, some studies in noncancer-related chronic pain patients yielded inconsistent results [57]. Nevertheless, depression and pain are highly correlated in cancer patients, especially those with advanced-stage disease [58]. The mechanisms underlying depression and pain are similar as they both stimulate glutamatergic and GABAergic neuronal pathways with the frontal cortex, anterior cingulate cortex, thalamus, and hippocampus [59]. However, the drug-drug interactions between antidepressant medications and chemotherapy resulting from cytochrome P450 metabolism raise concerns as they could compromise the effectiveness of anticancer treatment [60]. Our meta-analysis results may promote future research.

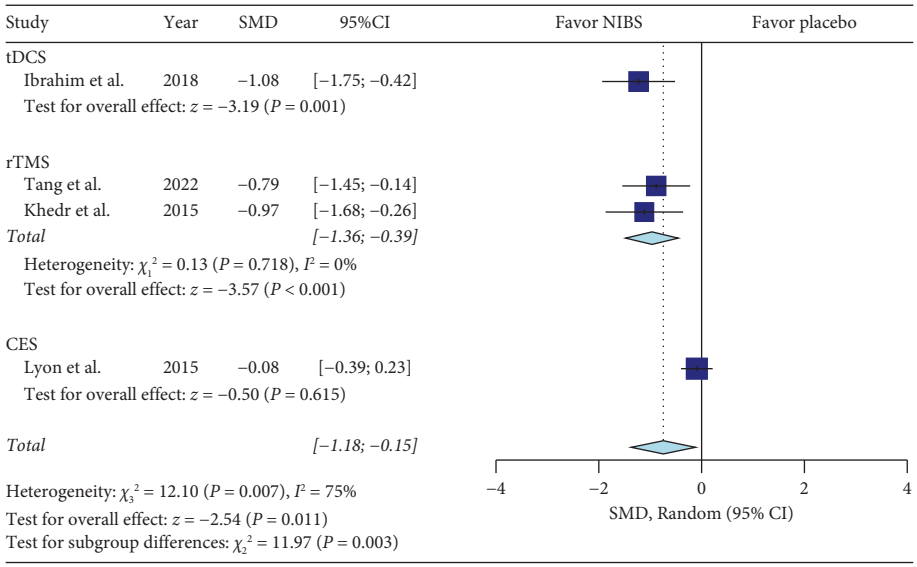

Figure 3: Forest plot of depression.

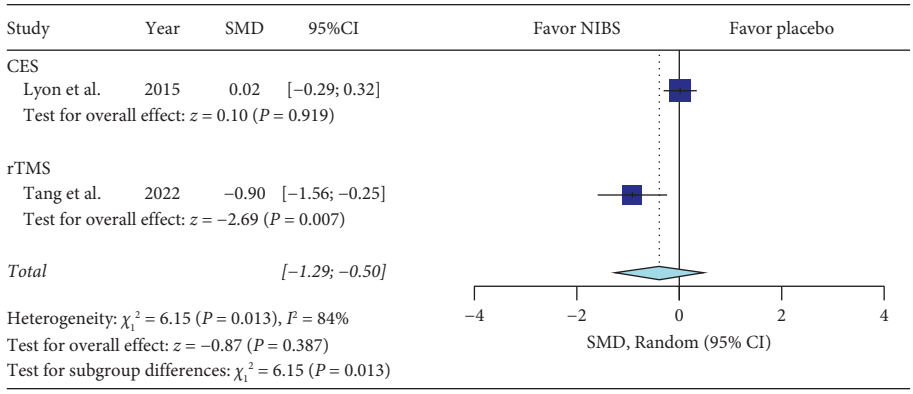

Figure 4: Forest plot of anxiety.

This study had several limitations. First, the number of studies included was limited. Although NIBS has been demonstrated to be effective for fibromyalgia, depression, and neuropathic pain, clinical studies focusing on cancer pain are limited [61–63]. However, the preliminary results of this meta-analysis support the use of NIBS in cancer pain management. Second, the NIBS technique and cancer type varied between studies. The included studies showed high heterogeneity in the outcomes of pain intensity, depression, and anxiety. The heterogeneity was reduced after grouping studies by NIBS for the preplanned subgroup analysis. This implies that the heterogeneity might originate from the type of NIBS applied. However, the included studies were also heterogeneous in study duration, cancer type, and NIBS target brain area. Despite the differences among studies, the mechanism by which NIBS targets centralized chronic pain involves a similar molecular pathway. Finally, the long-term effects of NIBS on cancer pain were not assessed in the present study; however, previous studies of NIBS on other etiologies of chronic pain showed pain reduction lasting from 6 months to nearly 3 years [64, 65].

5. Conclusion

NIBS, especially in the form of rTMS and tDCS, significantly improved depression symptoms. Only rTMS significantly improved cancer pain intensity in patients with nonbrain malignancy without severe adverse effects. Further studies are warranted to elucidate the long-term effects of NIBS on cancer pain.

Data Availability

The data supporting this meta-analysis are from previously reported studies and datasets, which have been cited.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Supplementary Table S1. Detailed search strategy. Supplementary Figure S2. Risk of bias summary and graph. Supplementary Figure S3. Influence analysis of pain intensity. Supplementary Figure S4. Influence analysis of depression. Supplementary Figure S5. Influence analysis of anxiety. (*Supplementary Materials*)

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