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REVIEW

Beta-Endorphin as a Biomarker in the Treatment of Chronic Pain with Non-Invasive Brain Stimulation: A Systematic Scoping Review

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Abstract: A scoping review to synthesize evidence and assess articles describing the use of beta-endorphins as a pain biomarker in chronic pain patients treated with non-invasive brain stimulation techniques was systematically performed with respect to the study quality, the technique employed and the results. Independent reviewers determined if the article met the study criteria at each stage for it to be included. Content analysis was applied and summarized. The results are described in a narrative form grouped by pain condition, type of intervention, stimulation protocol, outcome measures and main results. A total of 67 of 73 references were excluded, and 6 identified studies met the inclusion criteria. The study design, sample size, stimulation type, session protocol and the main findings of each study were extracted. The studies in this scoping review ranged from unsatisfactory to good based on the adopted criteria, with no study achieving an excellent rating. There is limited evidence on the dosage of beta-endorphin in chronic pain conditions during treatment with NIBS. Based on this literature, evidence suggests that BE may not only be useful for acute and persistent pain, but also for a variety of chronic pain states in which opioids are not effective.

Keywords: chronic pain, endorphin, electric stimulation, review

Introduction

Chronic pain affects 28% to 50% of the world population and its treatment remains a challenge,[1] with up to 30% of cases being resistant to drug treatment.[2] Despite advancement in available therapeutic resources, there is still no consensus on the mechanisms underlying the development and maintenance of pain.[3]

Non-invasive brain stimulation (NIBS) has been extensively studied for the past 30 years in controlling chronic pain.[2] Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) techniques are currently recommended for treating certain conditions such as fibromyalgia, neuropathic pain, complex regional pain syndrome and migraine, presenting low to moderate analgesic effect and without serious adverse events.[2,4,5] Other techniques investigated in treating pain include cranial electrotherapy stimulation (CES), transcranial random noise stimulation (tRNS) and reduced impedance non-invasive cortical electrostimulation (RINCE).[6,7]

The concept of "pain biomarkers" is sometimes used when discussing future treatment perspectives,[8] since control based on reported pain perception depends on the subjectivity of each patient, even when evaluated using multidimensional scales.[3] In this sense, pain medicine still lacks specific biomarkers of mechanisms

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which can predict some modulating degree of the descending inhibitory pathways of pain in order to guide diagnosis and treatment.[8] The recent "opioid epidemic" in the USA is an indication of the scarcity of effective and safe treatment options.[9]

Numerous neurotransmitters are involved in modulating nociceptive circuits, acting on structures of the brain stem (periaqueductal gray matter and the ventromedial rostral bulb) and the spinal cord.[8,10,11] Among these neurotransmitters, beta-endorphin (BE), an endogenous opioid, has not only been shown to have a comparable analgesic effect to morphine, but also to be 18 to 33 times more potent.[11] Nevertheless, mu opioid receptors (the main binding site of BE) are expressed by somatosensory neurons in the dorsal and trigeminal root ganglia, nociceptive neurons in the dorsal horn and multiple regions of the supraspinal segment.[10] BE preferentially acts as a ligand for mu receptors, which, like other membrane receptors of the endogenous opioid system, are coupled to an inhibitory G protein and stimulate intracellular signaling cascades which normally depress neural functions and are related to the inflammatory process characteristic of pain states.[10]

Thus, an extensive opioidergic network is perceived which is capable of interacting with other neurotransmitters and producing a general analgesic effect.[12] Research with non-opioid analgesic therapies which promote action by endogenous opioids may contribute to combat the current opioid epidemic.[10]

However, currently there is no definition on the clinical use of beta-endorphin as a biomarker in patients with chronic pain treated with NIBS techniques. A recent meta-analysis involving patients with chronic low back pain undergoing different physical rehabilitation techniques pointed out beta-endorphin as a potential therapeutic biomarker for clinical improvement.[13]

Thus, the objective of the present systematic scoping review is to evaluate and synthesize the evidence of beta-endorphin as a biomarker in the treatment of pain with non-invasive brain stimulation techniques providing an overview of the quality of the manuscripts, employed techniques and results.

Methods

A scoping review of articles describing the use of beta-endorphins as a pain biomarker in chronic pain patients treated with non-invasive brain stimulation techniques was systematically performed. The methodology for this review was based on the structure proposed by Arksey and O'Malley[14] and recommendations based on the work of Levac et al[15] and Peters et al.[16] In addition, this scoping review was conducted using a research strategy based on PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyzes extension for Scoping Reviews),[17] and previously registered on the OSF (Open Science Framework) support platform for scientific research under.[18]

The PubMed, Cochrane, Embase, PsychINFO and LILACS databases were searched from the beginning until May 2020 with the terms described in Table 1. The full texts of the selected studies were retrieved and independently evaluated in a standardized manner by two reviewers (CD and CM). These reviewers determined if the article met the study criteria at each stage for it to be included. For articles in which they disagreed, the reviewers checked and revised their criteria until reaching a final agreement. Reference lists of retrieved articles were also manually searched for additional articles.

Table 1 Terms Used in Locating Articles Investigating the Use of Beta-Endorphin as a Pain Biomarker in Chronic Pain Patients Treated with Non-Invasive Brain Stimulation Techniques. For the Sake of Simplicity, We Only Show the PubMed Database Search Strategy

Advanced search	"Title/Abstract"
PAIN terms	"pain" OR "ache"
Boolean search	AND
β-ENDORPHIN terms	"endorphin" OR "β-endorphin" OR "beta-endorphin" OR "beta-EP" OR "β-EP"
Boolean search	AND
NIBS terms*	"neuromodulation" OR "neurostimulation" OR "brain stimulation" OR "TMS" OR "rTMS" OR "transcranial magnetic stimulation" OR "tDCS" OR "DCS" OR "transcranial direct-current stimulation" OR "transcranial direct current stimulation" OR "CES" OR "TCES" OR "cranial electrotherapy stimulation" OR "transcranial electrical stimulation" OR "tACS" OR "transcranial alternating current stimulation" OR "tRNS" OR "RNS" OR "transcranial random noise stimulation" OR "RINCE" OR "reduced impedance non-invasive cortical electrostimulation" OR "reduced impedance noninvasive cortical electrostimulation"

Abbreviation: *NIBS, non-invasive brain stimulation.

Eligibility Criteria

The studies needed to be written in English and had to meet the following criteria: (1) empirical study; (2) involving patients diagnosed with chronic pain according to IASP (International Association for the Study of Pain) criteria;[19] (3) used a non-invasive brain stimulation technique as a therapeutic intervention; and (4) used beta-endorphin as an outcome measure.

Studies in healthy samples or interventions other than NIBS were excluded, including studies with electroconvulsive therapy as its mechanism of action substantially differs from other forms of brain stimulation,[7] and indirect forms of stimulation such as vestibular caloric stimulation and occipital nerve stimulation. Studies with invasive brain stimulation techniques with electrode implantation, as well as case studies, theoretical simulations and conference summaries were also excluded.

Quality Evaluation

A quality evaluation is included although it is not mandatory in the context of a scoping review, since the addition of this type of analysis provides greater accuracy in assessing the validity and methodological criteria of the included studies.[20] In this sense, a content analysis was applied and summarized in a table. The results are described in a narrative form grouped by pain condition, type of intervention, stimulation protocol, outcome measures and main results.

The Downs and Black[21] scale was used to evaluate the selected studies which consists of 27 questions related to methodological quality in the following domains: report (ten questions), external validity (three questions), internal validity - bias and variable confusion (13 questions) and statistical power (one question). This scale enables assessing the methodological quality of not only randomized clinical trials, but also non-randomized studies, in addition to providing a profile of the article, alerting reviewers to its methodological strengths and weaknesses. A modified version was used[22] which provides a maximum score of 28 points, in which each article can be classified with a score of "excellent" (24–28 points), "good" (19–23 points), "average" (14–18 points), or "unsatisfactory" (<14 points).[21,22]

Results

The search strategy identified a total of 73 references, of which 67 were excluded, including 6 articles of interest in this review (Figure 1). The reviewers identified the study design, sample size, stimulation type, session protocol and the main findings of each study (as described in Table 2).

The first study identified was by Gabis et al[23] who conducted a randomized, double-blind, placebo-controlled clinical trial in 20 patients with chronic low back pain (9 men and 11 women) treated with cranial electrotherapy stimulation (CES). They performed 30-minute sessions on eight consecutive weekdays (mode 3, 77 Hz frequency and 3.3 msec pulse width). Pain level (VAS) and serum BE were assessed before and after the first day of treatment. The authors concluded that CES is a safe technique and has a positive effect on serum BE levels, which can relieve chronic low back pain accompanied or mediated by the release of BE.

Following this investigation, Ahmed et al[24] conducted a randomized, double-blind, placebo-controlled clinical trial in 27 patients with phantom limb pain (19 men and 8 women) treated with rTMS (20 Hz, 80% RMT, 2000 pulses) over the M1 hand area contralateral to the painful side. Pain was assessed using the visual analogue scale (VAS) and the LANSS scale (Leeds assessment of neuropathic symptoms and signs) before and after the first session, after the fifth session, and after the first and second months of the last session. Serum BE was assessed before the first and after the fifth session. The authors suggested that long-term pain relief in patients with phantom pain may be related to an increase in BE level.

Misra et al[25,26] performed two similar non-randomized studies in the years 2013 and 2017 in patients with migraine and in healthy controls submitted to 3 alternate days of rTMS (10 Hz, 70% RMT, 600 pulses) applied on the left M1 hand area. The sample in the clinical trial conducted in 2013 consisted of 45 adults (11 men and 34 women). Clinical characteristics, including migraine duration, frequency, severity and functional disability, triggers, allodynia and number of analgesics used were noted. The plasma beta-endorphin level was estimated before the first rTMS session and after the third. They concluded that the serum BE level is reduced in migraine, especially in the chronic form, with its relief being associated with an increase in serum BE. Next, the sample in the following trial in 2017 was composed of 93 patients with migraine and 20 controls divided into 3 groups according to the sequence of the sessions performed: group I - 3 active sessions; group 2–1 active session followed by 2 sessions of simulated stimulation; and group II - 3 sessions of simulated stimulation. The BE level was measured before

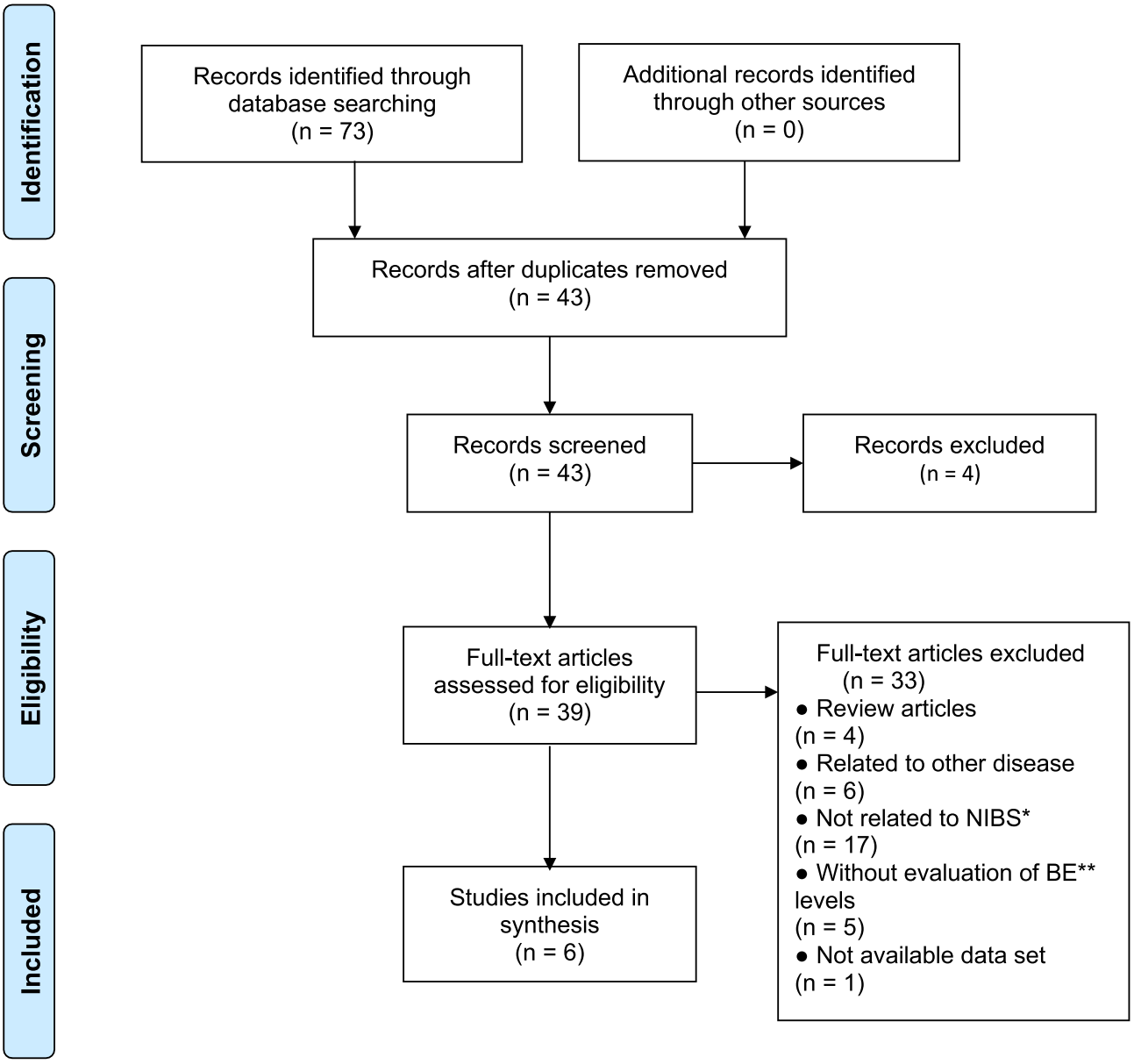

Figure 1 Flow diagram for study selection.
Abbreviations: *BE, beta-endorphin; **NIBS, non-invasive brain stimulation.

the first rTMS session and after the third. Improvement in headache frequency and severity was assessed at 1 month. They found that rTMS (10 Hz) relieves headache by increasing the BE level, with a post-stimulation value above 4 ng/mL associated with improved headache frequency.

In the same period, Khedr et al[27] conducted a randomized, double-blind, placebo-controlled clinical trial with data obtained from 36 patients (2 men and 34 women) diagnosed with primary fibromyalgia (ACR, 2010) treated with anodic tDCS (2 mA/35 cm2, 20 min) in 5 consecutive days applied over M1 on the left side. The BE level was measured before the first session of tDCS and after the tenth. As a result, about 38–39% reduction in different pain classification scales (WPI: Widespread Pain Index; SS: severity symptoms of fibromyalgia; VAS: visual analog scale) was observed in the experimental group at the end of treatment. Notably, there was also a parallel improvement in the depression and BE level. The authors concluded that pain relief after tDCS may be related to the release of BE.

Table 2 Characterization of the Studies Investigating the Role of BE Level in Chronic Pain Patients Treated with Non-Invasive Brain Stimulation Techniques

Study	Design			Pain Condition	Number of Participants Average Age (Years) Gender Distribution	Stimulation Protocol		
	Random	Control	Blinding			Type of Stimulation and Parameters	Site	Number of Sessions
	Main findings related to BE							
Gabis, Shklar, & Geva, 2003[23]	YES	YES	YES	Chronic back pain	20 10 in active group: 45.80 (20–77) 10 in control group: 46.70 (27–69) 9 males and 11 females	CES biphasic, 77 Hz, maximal current: 4 mA for 30 min	Mode 3 (forehead and behind each ear area)	8 consecutive weekdays
	CES relieves chronic back pain accompanied or mediated by BE release							
Ahmed, Mohamed, & Sayed, 2011[24]	YES	YES	YES	Phantom pain	27 17 in active group: 52.01 ± 12.7 10 in sham group: 53.3 ± 13.3 19 males and 8 females	rTMS 20 Hz, 80% RMT, 2000 pulses	M1 hand area contralateral to the painful side	5 consecutive days
	BE was increased significantly after real stimulation with no changes in patients who received sham **Long lasting pain relief in patients with phantom pain might be related to an elevation of BE level**							
Misra, Kalita, Tripathi, & Bhoi, 2013[25]	NO	YES	NO	Migraine	45 25 migraine patients: 35 (20–65) 20 healthy controls: 37 (18–55) 11 males and 34 females	rTMS 10 Hz, 70% RMT, 600 pulses	Left M1 hand area	3 alternate days
	BE is reduced in migraine which is more marked in chronic migraine compared to episodic migraine **BE level is increased following high rate rTMS** **Rise in BE following rTMS is associated with migraine relief**							
Misra, Kalita, Tripathi, & Bhoi, 2017[26]	NO	YES	NO	Migraine	113 93 migraine patients: 33.3 ± 10.1 20 healthy controls: 34.2 ± 10.0 58 males and 34 females	rTMS 10 Hz, 70% RMT, 600 pulses	Left M1 hand area	3 alternate days
	10 Hz rTMS relieves headache by increasing BE level **BE level above 4 ng/mL is critical in headache relief irrespective of type of rTMS**							
Khedr et al, 2017[27]	YES	YES	YES	Fibromyalgia	36 18 in active group: 31.3 ± 10.99 18 in sham group: 33.89 ± 11.18 2 males and 34 females	tDCS anodal, 2 mA for 20 min	C3 region	10 5 consecutive days/week for 2 weeks.
	Changes in serum BE level correlated will with the changes in different rating scales of pain and mood **Pain relief after tDCS could be related to endorphin release**							
Suchting, Colpo, Rocha, & Ahn, 2020[28]	YES	YES	YES	Knee Osteoarthritis	40 20 in active group: 60.6 ± (9.8) 20 in sham group: 59.3 ± (8.6) 19 males and 21 females	tDCS anodal, 2 mA for 20 min	C3 or C4 region contralateral to the affected knee	5 consecutive days.
	Active tDCS (as compared to sham tDCS) is associated with reduced levels of IL-6, IL-10, TNF-α, and BE **Treatment with active tDCS may have therapeutic benefits over and above sham tDCS for reducing inflammation in patients with knee OA**							

Abbreviations: BE, β-endorphin; C3, left M1; C4, right M1; CES, cranial electrical stimulation; IL, interleukin; M1, primary motor cortex; OA, osteoarthritis; tDCS, transcranial direct-current stimulation; TNF- α, tumor necrosis factor- α; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation.

More recently, Suchting et al[28] conducted a randomized, double-blind, placebo-controlled clinical trial with data obtained from 40 patients with knee osteoarthritis treated with tDCS (2 mA/35 cm2, 20 min) on 5 consecutive days applied to the M1 region contralateral to the affected knee. The following stress and inflammation markers were measured: IL-6, IL-10, TNF-α, PCR, cortisol and BE. The BE level was measured before the first session of tDCS and after the fifth. The authors found that active tDCS is associated with a reduction in inflammation levels, as active patients (relative to sham) presented reduced inflammatory cytokines and BE levels.

Quality Evaluation

The studies in this scoping review ranged from unsatisfactory to good based on the criteria of Downs and Black,[21] with no study achieving an excellent rating.[22] The detailed scores for each study are shown in Table 3. All three studies with good quality methodological classification were randomized clinical trials.[23,27,28] Another randomized study obtained average quality,[24] and two observational studies were considered unsatisfactory.[25,26] The reporting domain was well scored in most studies, with the most common failures in questions regarding the reporting of the main confounding factors, possible adverse events and characteristics of patients lost during follow-up. No study was scored in the external validity domain, generally because the answers were indeterminate. The internal validity scores were high in randomized studies.[23,24,27,28] Biases related to the lack of outcome blinding of evaluators and the failure to investigate the main confounding factors contributed to low scores in that domain in observational studies.[25,26] No study described power calculations showing enough power to detect a clinically important effect.

Discussion

There are few published studies generally evaluating BE as a response biomarker in treating chronic pain with the NIBS techniques. Six studies were identified which met the inclusion criteria.[23–27] This scoping review revealed two important findings: (1) there is limited evidence on the dosage of beta-endorphin in chronic pain conditions during treatment with NIBS; and (2) the quality of the studies was good in 3/6 manuscripts based on criteria of Downs and Black.[21]

The evidence for BE measurement in clinical practice is still uncertain with few adequately controlled studies with long-term follow-up after neurostimulation sessions. Five studies were identified with promising results in which the increase in BE levels was associated with improvement in pain assessment.[23–27]

Regarding the response prediction to neurostimulation related to BE rates, none of the studies included in this review present considerations about possible confounders related to the response rates and adjustments made to control these variables. Some studies found low pretreatment BE levels in patients with chronic pain compared to healthy controls,[24–26] which would explain the persistence of pain in this population and clinical improvement after the sessions. Evidence indicates that a lower BE level at the baseline may explain greater pain intensity,[13] and that high BE values are associated with less endogenous opioid analgesia.[29]

Interestingly, one study found a significant increase in BE associated with improvement in pain scales and mood in the control group, although with greater effect size for the treatment group.[27] This finding also raises the participation of the endogenous opioid system in placebo analgesia, probably mediated by affective and cognitive aspects.[30,31]

Although the techniques described in these studies (tDCS, rTMS and CES) have different routes and action mechanisms, all aim to induce depolarization mechanisms in an attempt to reduce chronic pain, directly altering brain activity in an extensive neuronal network involved in pain processing,[7] herein highlighting (for example) evidence of the participation of endogenous opioids in the subsequent effects of active stimulation with tDCS and rTMS.[32,33] All studies with tDCS and rTMS used the primary motor cortex as a target for stimulation with an increase in BE after treatment, including an association with the improvement of clinical and physiological parameters.[24–28] It is possible that there are common activation mechanisms of the endogenous opioid system with these techniques applied in M1. Imaging studies in humans suggest that stimulation modulate pain from a likely entry point in the thalamus, as well as by facilitating the descending inhibitory pain mechanisms.[7,34]

Previous evidence with invasive techniques (for example, epidural stimulation of the motor cortex) points to long-term pain relief in both patients and animal models.[35] Future studies with NIBS should prioritize

Table 3 Checklist for Quality Assessment

	Gabis, Shklar, & Geva, 2003[23]	Ahmed, Mohamed, & Sayed, 2011[24]	Misra, Kalita, Tripathi, & Bhoi, 2013[25]	Misra, Kalita, Tripathi, & Bhoi, 2017[26]	Khedr et al, 2017[27]	Suchting, Colpo, Rocha, & Ahn, 2020[28]
REPORTING*	**Israel & USA**	**Egypt**	**India**	**India**	**Egypt & Germany**	**USA**
Q_1 Hypothesis/aim/objective clearly described	0	1	1	1	1	1
Q_2 Main outcomes in Introduction or Methods	1	1	1	1	1	1
Q_3 Patient characteristics clearly described	1	1	1	1	1	1
Q_4 Interventions of interest clearly described	1	1	1	1	1	1
Q_5 Principal confounders clearly described	0	0	0	0	0	2
Q_6 Main findings clearly described	1	1	1	1	1	1
Q_7 Estimates of random variability provided for main outcomes	1	1	1	1	1	1
Q_8 All adverse events of intervention reported	1	0	0	0	1	0
Q_9 Characteristics of patients lost to follow-up described	1	0	0	0	1	0
Q_10 Probability values reported for main outcomes	1	1	1	1	1	1
EXTERNAL VALIDITY						
Q_11 Subjects asked to participate were representative of source population	0 UTD	0 UTD	0 UTD	0 UTD	0 UTD	0 UTD
Q_12 Subjects prepared to participate were representative of source population	0 UTD	0 UTD	0 UTD	0 UTD	0 UTD	0 UTD
Q_13 Location and delivery of study treatment was representative of source population	0	0	0	0	0	0
INTERNAL VALIDITY – BIAS & CONFOUNDING VARIABLES						
Q_14 Study participants blinded to treatment	1	1	0	0	1	1
Q_15 Blinded outcome assessment	1	1	0	0	1	1
Q_16 Any data dredging clearly described	1	1	1	1	1	1
Q_17 Analyses adjusted for differing follow-up lengths	1	1	0 UTD	0 UTD	1	1
Q_18 Appropriate statistical tests performed	1	1	1	1	1	1
Q_19 Compliance with interventions was reliable	1	1	1	1	1	1
Q_20 Outcome measures were reliable and valid	1	1	1	1	1	1
Q_21 All participants recruited from the same source population	1	1	1	1	1	1
Q_22 All participants recruited over the same time period	1	1	1	1	1	1
Q_23 Participants randomized to treatment(s)	1	1	0	0	1	1
Q_24 Allocation of treatment concealed from investigators and participants	1	1	0	0	1	1
Q_25 Adequate adjustment for confounding variables	0	0	0	0	0	1
Q_26 Losses to follow-up taken into account	1	0 UTD	0 UTD	0 UTD	1	0 UTD
POWER						
Q_27 Sufficient power to detect treatment effect at significance level of 0.05	0	0	0	0	0	0
TOTAL	**20**	**18**	**13**	**13**	**21**	**21**

Note: *Reporting items adapted from Downs and Black.[21]
Abbreviation:*UTD, Unable to determine.

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motor cortex stimulation and pay attention to medium and long-term follow-up.

Interestingly, another study was identified which pointed to an improvement in inflammation markers in patients with knee osteoarthritis associated with a decrease in BE.[28] This distinct result suggests yet another applicability of NIBS not directly related to the subjective perception of chronic pain, but to possible molecular and cellular mechanisms of underlying central and peripheral sensitization.[36]

Although the activation of the pathways that originate in the brainstem is involved in the process of transmitting the nociceptive sensation, this control does not seem to be exclusive to the descending inhibitory pathways.[37] There is evidence that stimulating the primary motor cortex and the prefrontal cortex are capable of causing changes in the thalamus, anterior cingulate and insula activity,[38] leading to a consequent increase in the release of opioids from various brain structures that process pain.

Previous studies indicate that the low BE level at baseline and its significant increase after brain stimulation suggest a state of chronic hypoendorphinemia reported in some painful conditions, such as trigeminal neuralgia and rheumatoid arthritis,[39,40] which is modulated with the release of circulating BE after treatment.[24] Since plasma BE primarily originates from the pituitary and immune cells and its regional distribution correlates with the levels of opiate receptors, its association with pain pathways indicates that it is configured as an important neurotransmitter involved in the response to systemic stress.[13]

Thus, the increase in BE after non-invasive neurostimulation may be associated with the release of cortisol and other neurotransmitters, and its process can be regulated by electrical stimuli used to modulate pain in cortical and subcortical areas with mediation of the hypothalamic-pituitary axis.[25,26]

Regarding the quality of the manuscripts, we identified methodological limitations with most studies which led to an uncertainty of the reported findings or results. Although the studies evaluated the pre- and post-intervention results, there was no measurement of BE after the follow-up period. Most performed the final measurement immediately after the end of the last session, except for one study in which they performed it after the first session.[23] There was at least one correlation in the variation of serum BE with some clinical variable in the treatment group in all studies. However, a good quality RCT with a longer intervention period also observed a correlation in the control group.[27] The lack of a control group of healthy individuals was a common finding in half of the articles included in this review.[23,27,28]

Although the present study raises important considerations in the scope of neurostimulation and the role of beta-endorphin as a response predictor, some limitations must be considered. The review was limited to peer-reviewed publications in English, which may have led to the omission of some articles. Regarding the methodological quality assessment, the Downs and Black criteria have equal weights for each item.[22] This weighting may inadvertently result in a lower score, especially for non-randomized study designs.[41]

Conclusion

In this scoping review, current evidence suggests that serum BE measurement may not only be useful for acute and persistent pain, but also for a variety of chronic pain states. Future studies evaluating BE as a response biomarker in treating chronic pain with NIBS should prioritize motor cortex stimulation and pay attention to medium and long-term follow-up.

Author Contributions

SA and EB conceived of the study and led the design, analysis, and drafting of the manuscript. CD and CM conducted data collection and analysis. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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The authors have no conflicts of interest to report for this work.

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