Review

Central nervous system stimulation therapies in phantom limb pain: a systematic review of clinical trials

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Abstract

Phantom limb pain is a chronic pain syndrome that is difficult to cope with. Despite neurostimulation treatment is indicated for refractory neuropathic pain, there is scant evidence from randomized controlled trials to recommend it as the treatment choice. Thus, a systematic review was performed to analyze the efficacy of central nervous system stimulation therapies as a strategy for pain management in patients with phantom limb pain. A literature search for studies conducted between 1970 and September 2020 was carried out using the MEDLINE and Embase databases. Principles of The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline were followed. There were a total of 10 full-text articles retrieved and included in this review. Deep brain stimulation, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and motor cortex stimulation were the treatment strategies used in the selected clinical trials. Repetitive transcranial magnetic stimulation and transcranial direct current stimulation were effective therapies to reduce pain perception, as well as to relieve anxiety and depression symptoms in phantom limb pain patients. Conversely, invasive approaches were considered the last treatment option as evidence in deep brain stimulation and motor cortex stimulation suggests that the value of phantom limb pain treatment remains controversial. However, the findings on use of these treatment strategies in other forms of neuropathic pain suggest that these invasive approaches could be a potential option for phantom limb pain patients.

Key Words: central nervous system stimulation; neuromodulation; neuropathic pain; phantom limb pain; systematic review

Introduction

Phantom limb pain (PLP) is characterized as the painful sensation experienced in the missing limb after amputation. PLP is an acute example of deafferentation pain, which may be attributed to other conditions such as peripheral nerve injury, spinal cord injury or avulsions of the brachial plexus. Moreover, somatosensory system reorganization in particular is associated with this deafferentation pain (Nardone et al., 2019).

It is necessary to differentiate PLP from other types of sensation in patients with amputees such as stump pain or phantom limb sensation. In this manner, the first would be the pain perceived in the amputation stump, while the phantom limb sensation would be the feeling of missing limb but for pain (Collins et al., 2018). PLP is therefore a syndrome which is related to healthcare and economic costs and may have a profound effect on the wellbeing (Giummarra and Moseley, 2011).

Published PLP rates range from 50% to 80% of limb amputees, with 5–10% of these individuals experiencing extreme pain (Batsford et al., 2017; Yin et al., 2017). Variations in prevalence are based on preamputation pain, amputation location, anesthetic and surgical procedure, sex, psychological factors, and time after amputation (Richardson et al., 2015; Aiyer et al., 2017). Literature indicates that majority of amputees suffer PLP in the year following their amputation, but with time declines from 72% at 8 days, 65% at 6 months and 59% at 2 years (Collins et al., 2018). Likewise, there are lower prevalence rates of phantom pain over time, 32% at 6 months, 26% at 1 year and a half, 23% at 2 years and a half and 27% at 3 years and a half after amputation (Bosmans et al., 2010). Recommended prevention measures include the use of local epidural or perineural postoperative anesthetics, precautions to protect peripheral nerves during surgery and the importance of early recovery (Knotkova et al., 2012).

PLP is a complicated form of pain that is often identified as neuropathic pain and, despite its presence in the literature since 1551, the exact mechanisms underlying it are not well understood. In this sense, the key mechanisms indicated in the literature appear to be central nervous system sensitization, peripheral nerve injury and cortical reorganization (Batsford et al., 2017). According to previous studies, a maladaptive plastic reorganization of the somatosensory system may be directly related to PLP (Flor et al., 2006), involving increased corticospinal neuron excitability and decreased GABA activity in the primary motor cortex (Collins et al., 2018). This theory suggests that PLP is primarily due to the primary

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somatosensory cortex (S1) reorganization, which may be characterized by functional degradation of the limb's missing representation and restoration of other representations of the part of the body (Kikkert et al., 2018; Valyear et al., 2020). Some authors have described an invasion of the lip representation in the homunculus of amputees towards the missing hand cortex, using a surface-based method, demonstrating preserved involvement of the phantom hand in the territory of amputees' missing hands. However, this change was only partial and did not constitute a complete invasion of the lips into the territory of the hand, so no statistical correlation between the cortical reorganization and the PLP could be established (Makin et al., 2015). Conversely, other factors, such as peripheral factors, including nociceptive inputs from the residual limb, have also been correlated with PLP (Flor et al., 2006), as well as psychological factors, which can influence the duration and pain intensity (Urits et al., 2019).

This lack of knowledge of the processes of PLP is expressed in the absence of clear interventions to assist its management. In fact, PLP is potentially one of the most complex chronic pain management syndromes. Thus, PLP treatment includes both pharmacological control, noninvasive nonpharmacological strategies and invasive treatments (Luo and Anderson, 2016).

In this line, pharmacological agents that are commonly used to avoid or reverse cortical reorganization are anticonvulsants, tricyclic antidepressants, and other agents such as N-methyl-D-aspartate receptor antagonists (e.g. ketamine) (Alviar et al., 2016). The efficacy of most treatments is extrapolated from the positive outcomes of other neuropathic pain syndromes, but not from PLP-controlled trials (Knotkova et al., 2012). The last Cochrane revision (Alviar et al., 2016) supports this idea, which concludes that the short- and long-term efficacy of pharmacological agents in the treatment of PLP remains unclear.

On the other hand, a wide range of noninvasive nonpharmacological PLP treatments have been documented in the literature, including sensory discrimination training, transcranial direct current stimulation (tDCS), cognitive behavioral therapy, electrotherapy, repetitive transcranial magnetic stimulation (rTMS) and visual feedback, which is known as mirror box therapy (Batsford et al., 2017; Aternali and Katz, 2019). However, high-quality randomized controlled trials to direct treatment development of nonpharmacological conservative treatments are hardly established (Batsford et al., 2017).

Lastly, invasive therapies are known to be the final recourse for patients who have failed all noninvasive treatments. PLP-mechanisms are guided by neuromodulatory techniques which specifically address maladaptive central neuroplastic changes in brain pain-processing networks or the Pain Matrix. Deep brain stimulation (DBS), motor cortex stimulation (MCS), and spinal cord stimulation are the principal invasive therapies used (Knotkova et al., 2012).

Little is known about randomized controlled trials to support treatment choices for this narrow range of approaches. We decided to explore the evidence of noninvasive nonpharmacological and invasive PLP management strategies, and therefore a systematic review was conducted to analyze the efficacy of central nervous system stimulation therapies for pain management in people with PLP.

Data and Methods

A systematic review of clinical trials was performed using MEDLINE and Embase databases for studies published between 1970 and September 2020. Principles of The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher et al., 2010) were followed to perform this review. The aim of the study is to understand whether central nervous system stimulation is an effective strategy in patients with phantom limb pain. The protocol was not registered for this review.

The literature search strategy used was a combination of "natural language" and "structural language" (**Table 1**), structured by Patient-Intervention-Comparison-Outcome (PICO) research question. The snowball method was then conducted using citation analysis and bibliography scanning.

Table 1 | **Search strategy**

	Natural language	MeSH	EMTREE
Patient	Phantom limb syndrome	Phantom limb pain, Phantom limb	Phantom pain
Intervention	Spinal cord stimulation Deep brain stimulation Cortex stimulation Magnetic stimulation Electric stimulation	Spinal cord stimulation Deep brain stimulation Motor cortex Transcranial magnetic stimulation Electric stimulation	Spinal cord stimulation Brain depth stimulation Motor cortex stimulation Transcranial magnetic stimulation Electrostimulation
Outcome	Outcomes keywords were excluded in definite searches because they limit much of the research available, while our goal was to investigate all the effects mentioned in the literature		

Specific search strategy

PubMed: ((((((“Phantom limb syndrome”[Title/Abstract]) OR “phantom limb”[MeSH Terms]) OR pain, phantom limb[MeSH Terms])))))) AND ((((((((((((((“spinal cord stimulation”[Title/Abstract]) OR “spinal cord stimulation”[MeSH Terms]) OR “deep brain stimulation”[Title/Abstract]) OR “deep brain stimulation”[MeSH Terms]) OR “cortex stimulation”[Title/Abstract]) OR “motor cortex”[MeSH Terms]) OR “magnetic stimulation”[Title/Abstract]) OR “transcranial magnetic stimulation”[MeSH Terms])))) OR electric* stimulation [Title/Abstract]) OR “electric stimulation”[MeSH Terms]).

Embase: (‘phantom limb pain’:ab,ti OR ‘phantom pain’/de) AND ‘spinal cord stimulation’:ab,ti OR ‘spinal cord stimulation’/exp OR ‘deep brain stimulation’:ab,ti OR ‘brain depth stimulation’/exp OR ‘cortex stimulation’:ab,ti OR ‘motor cortex stimulation’/exp OR ‘magnetic stimulation’:ab,ti OR ‘transcranial magnetic stimulation’/exp electric* stimulation:ab,ti OR ‘electrostimulation’/exp.

Study eligibility criteria

The exclusion criteria were non-English studies and peripheral nervous system stimulation studies. Therefore, all human clinical trials in adult populations, including phantom limb pain and central nervous system stimulation, were included in the English literature from January 1970 to September 2020.

Study selection and methodologic quality

Two reviewers (MAG and PR) applied eligibility criteria in each database. Next, the studies were chosen by these two reviewers who evaluated all studies separately and in duplicate. If consensus could not be found, a third reviewer (DC) was included. All reviewers discussed the selected data and addressed the extracted data.

The Jadad Scale for Reporting Randomized Controlled Trials checklist was used to review the papers in order to determine the quality of RCTs in a simple manner. This is a scale of five simple items, which has known reliability and external validity. A score below 3 points indicates low quality based on the quality of randomization, double blinding, and drop-outs extracted of each study (Roman et al., 2018).

Data extraction and data synthesis

The following are the main categories of the coded variables: reference, number of patients and controls, intervention, localization and duration of treatment, and finally, the scale to evaluate pain relief and the results and conclusions of the studies.

Results

In the initial search, 303 studies were extracted to be screened, excluding duplicate citations. Titles of the articles were analyzed and after excluding reviews and observational articles, 93 studies were selected. To apply the eligibility criteria, titles and abstracts of these papers were screened. Finally, 10 full-text papers were used in the review and included in the final manuscript (**Figure 1**).

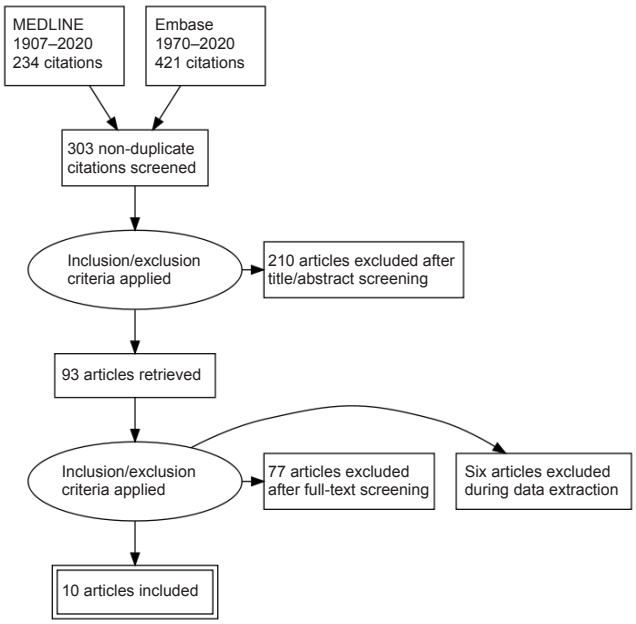

Figure 1 | **PRISMA flow chart of phantom limb pain and central nervous system stimulation.**

In **Table 2**, a total of 10 studies were reviewed, which are chronologically sorted. Of the 10 studies analyzed, four of them used both rTMS and tDCS, and the other two reports used DBS and MCS. All of the research reviewed included patients with an amputation who reported PLP; and most of the studies used the visual analogic scale (VAS) to test their results.

All the papers contained a total of 281 patients and controls. In each study, the number of participants ranged, from five participants in the smallest study (Nardone et al., 2015) to 56 participants in the biggest (Rasche et al., 2006). In addition to PLP, other forms of pain such as spinal cord injury or post stroke were included in some studies (Saitoh et al., 2003; Rasche et al., 2006; Antal et al., 2010; Muniswamy et al., 2016). 50% of the studies were conducted in Europe (UK, Germany and Italy), 30% in USA and 20% in Africa (Egypt) and Asia (Japan) respectively.

Based on the Jadad Scale for Reporting Randomized Controlled Trials, four of them are classified as high quality (**Table 3**).

Discussion

This systematic review aimed to analyze the efficacy of central nervous system stimulation therapies for pain management in people with PLP. Ten randomized controlled trials were included in the final review. 173 amputees treated for PLP were included with the following interventions: rTMS, tDCS, DBS and MCS.

Non-invasive treatments

rTMS is one of the most investigated method, with the 40% of the clinical trials analyzed. TMS induce lasting modulation effects on brain activity, transmitted as sets of pulses or a single pulse (rTMS) through a strong magnetic field supplied with a magnetic coil over the scalp (Canavero et al., 2002). Our review found that rTMS was effective to decrease pain sensation in PLP (Ahmed et al., 2011; Malavera et al., 2013, 2016). Furthermore, serum beta-endorphin significantly increased after treatment (Ahmed et al., 2011), and symptoms of anxiety and depression showed substantial reductions in patients receiving real rTMS in two of the reports (Ahmed et al., 2011; Malavera et al., 2016) compared with patients who received simulated rTMS or placebo.

The first clinical trial involving rTMS was published in 2003 (Töpper et al., 2003), which investigated how pain syndromes can be influenced by rTMS. The patients were two subjects with a unilateral lower cervical root avulsion and chronic arm pain. The acute effects of rTMS in four healthy subjects with induced pain (cold water immersion of the right hand) were studied as a control. Stimulation of the contralateral parietal cortex led to a decrease in pain intensity of up to 10 minutes, but there was no clear effect on pain in other cortical areas. However, trains used for 3 consecutive weeks on the contralateral parietal cortex did not result in lasting improvements in pain levels. Whereas the use of rTMS in the treatment of PLP is not confirmed by these findings, they underpinned the concept that phantom pain in the parietal cortex is due to dysfunctional activity.

The next clinical trial was done in 2011 (Ahmed et al., 2011) and included 27 patients with PLP for unilateral amputation (11 patients had upper limb amputation and 16 patients had below knee amputation).

For 5 consecutive days, 17 patients received 10 minutes of real rTMS over the hand region of motor cortex M1 every day and 10 patients received sham stimulation. In patients who received real rTMS, VAS and LANSS scores decreased significantly compared to those who received sham rTMS. Moreover, depression and anxiety levels in Hamilton scale showed a significant decrease in real rTMS patients. Finally, beta-endorphin was assessed 1 to 2 hours after five sessions and significantly increased after real stimulation, with no significant change in patients receiving sham rTMS. Thus, they concluded that pain relief could be attributed to an increase in serum beta-endorphin levels.

Lastly, the most recent studies involving rTMS and PLP were the group of Malavera and collaborators, who published their first findings in 2013, analyzing the efficacy of rTMS in the treatment of PLP in landmines victims (Malavera et al., 2013). Out of 49 patients, 26 subjects received real rTMS over the M1 contralateral hand to the amputated leg and 23 subjects received sham stimulation. The percentage change in VAS did not show significant differences at 15 or 30 days when both groups were compared. However, a significant difference was noted in the proportion of subjects with a decrease in VAS by more than 30% at 15 days in the active group versus sham, and a pattern was observed at 30 days. The last clinical trial of the same research group was published in 2016 and enrolled 54 patients (Malavera et al., 2016). Their findings showed that the administration of active rTMS caused significantly higher pain relief 15 days after treatment compared to placebo stimulation, although this effect was not significant 30 days after treatment. In addition, 70.3% of participants in the active group experienced a clinically significant pain relief (> 30%), compared to 40.7% in the sham group. Likewise, anxiety and depression symptomatology were analyzed as this aspect may be considered a confounder of pain relief, revealing the main impact of time without significant differences between treatment effects groups.

Table 2 | **Characteristics of studies included**

References	Participants	Methods	Interventions	Duration	Scales	Results
Kikkert et al. (2019)	17 patients with PLP and 15 controls	tDCS	- Patients: Anodal tDCS over the S1/M1 missing hand cortex and cathodal over the contralateral supraorbital area. - Controls: S1/M1 and the contralateral supraorbital region over the intact hand	4 sessions	SPQ	A single intervention session substantially eased PLP, with results lasting for at least 1 wk. PLP relief due to decreased activity in the S1/M1 missing hand cortex after stimulation
Malavera et al. (2016)	54 patients with PLP	rTMS	Real or sham rTMS of M1 (n = 27 in the active group and n = 27 in the sham group)	15 d	VAS	VAS reduction compared to sham stimulation: –53.38 ± 53.12% *vs*. –22.93 ± 57.16%; P = 0.03
Muniswamy et al. (2016)	9 patients (PLP, CRPS, or neuropathic pain following SCI)	tDCS	Group 1 (n = 3): anodal tDCS over DLPFC Group 2 (n = 3): anodal tDCS over M1 Group 3 (n = 3): sham tDCS over M1	10 d	McGill Pain Questionnaire	Group 1 subjects showed more progress on the McGill Pain Questionnaire than group 2 or group 3 subjects
Malavera et al. (2013)	49 patients with PLP	rTMS	Real or sham rTMS of M1 (n = 26 real rTMS over the hand area of M1 and n = 23 patients received sham)	No data	VAS	Percentage change of VAS at 15 d showed no significant differences The proportion of subjects with a decrease greater than 30% in VAS at 15 d in the active group *vs*. placebo showed significant differences
Bolognini et al. (2013)	8 patients with PLP	tDCS	Real or sham tDCS in the M1 and in the PPC	1 session	VAS	A selective short-lasting decrease of PLP was induced by anodal tDCS of M1 A selective short-lasting decrease of nonpainful phantom sensations was induced by cathodal tDCS of PPC
Ahmed et al. (2011)	27 patients with PLP	rTMS	Real or sham rTMS of M1 (n = 17 real rTMS over the hand area of M1 and n = 10 patients received sham)	5 d	VAS LANSS	Pain ratings at time points showed significant decrease (5 sessions, 1- and 2-mon follow-up) after real rTMS compared with baseline (P = 0.001), sham patients showed no significant changes
Antal et al. (2010)	21 patients with neuropathic pain syndromes (n = 1 with PLP)	tDCS	n = 12: anodal and sham tDCS in M1 n = 9: only anodal or sham tDCS in M1	5 d	VAS and cortical excitability measured by TMS	A greater enhancement was led by anodal tDCS in VAS ratings than sham tDCS, even 3–4 wk post-treatment
Rasche et al. (2006a)	56 patients with neuropathic pain syndromes (n = 4 with PLP)	DBS	In each patient: two leads (PVG and lateral somatosensory thalamus [VPL or VPM]) Both leads: subthreshold stimulation (0.5–1 V below threshold), half of the intensity of subthreshold stimulation, and placebo stimulation (intensity set to zero).	7 d	VAS	4 patients with PLP: 2 patients: 25–100% pain relief 2 patients: no pain relief
Töpper et al. (2003)	2 patients with PLP and 4 controls	rTMS	rTMS in various cortical sites in patients. rTMS in various cortical sites in experimentally induced pain controls	3 wk	VAS	No permanent changes in pain intensity were observed when both 1 and 10 Hz rTMS trains were applied to the contralateral parietal cortex. Normal subjects showed no influence by rTMS when experimental pain was induced
Saitoh et al. (2003)	19 patients with neuropathic pain syndromes (n = 2 with PLP)	MCS	Grid electrode place position: - Interhemispheric fissure - Central sulcus - Precentral gyrus	6–50 mon	VAS and Mc Gill Pain Questionnaire	In test stimulation, 14 patients experienced varying degrees of pain management The optimal stimulation point for pain relief was area 4 within the central sulcus

CRPS: Complex regional pain syndrome; DBS: deep brain stimulation; DLPFC: dorsolateralprefrontal cortex; EMOST: Electromagnetic-Own-Signal-Treatment; LANSS: Leeds assessment of neuropathic symptoms and signs; M1: primary motor cortex; NRS: numerical rating scale; PLP: phantom limb pain; PPC: posterior parietal cortex; PVG: periventricular gray region; S1: primary sensory cortex; SCI: spinal cord injury; SPQ: short pain questionnaire; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; VAS: Visual Analogue Scale; VPL: ventral posterior lateral nucleus; VPM: ventral posterior medial nucleus.

tDCS is the other more studied noninvasive treatment for brain stimulation, which was evaluated in the 40% of clinical trials included (Antal et al., 2010; Bolognini et al., 2013; Muniswamy et al., 2016; Kikkert et al., 2019). This procedure is based on the application to the scalp of a mild direct current flowing between two relatively large electrodes and penetrating the skull to reach the brain (Bolognini et al., 2013). This current modulates the degree of excitability and the firing rate of individual neurons when provided continuously for many minutes by changing the threshold of the neuronal resting membrane, causing long-lasting effects secondary to synaptic changes (Fritsch et al., 2010). The analgesic effect of five consecutive days of anodal/sham tDCS was demonstrated in a clinical trial in 2010 (Antal et al., 2010) in 21 patients, just 1 of them with PLP. Anodal tDCS led to a higher increase in VAS scores than sham tDCS, which was evident even three to four weeks after treatment. In 2013, the effects of a single session of M1 tDCS and posterior parietal cortex (PPC) on stump pain and nonpainful phantom limb sensations were measured in another clinical trial (Bolognini et al., 2013). Interestingly, their findings showed that PLP was correlated with increases in cortical excitability in the sensorimotor network and hyperexcitation of PPC was associated with nonpainful phantom sensations. In other words, through anodal tDCS in M1 they achieved an antalgic effect on PLP in increasing excitability in this system; and cathodal tDCS stimulation on PPC was correlated with enhancing nonpainful sensations. A study in 2016 investigated the best location for the use of tDCS and whether these locations were superior to placebo (Muniswamy et al., 2016). Nine patients with PLP, complex regional pain syndrome and neuropathic pain after spinal cord injury were enrolled. After intervention, the McGill Pain Questionnaire improved more in patients in the anodal DLPFC group than in patients who received sham tDCS to M1 or anodal tDCS to M1. In this study, they attempted to investigate the effect of the intervention on the quality of life

Table 3 | **Jadad Scale for Reporting Randomized Controlled Trials**

	Kikkert et al. (2019)	Malavera et al. (2016)	Muniswamy et al. (2016)	Malavera et al. (2013)	Bolognini et al. (2013)	Ahmed et al. (2011)	Antal et al. (2010)	Rasche et al. (2006a)	Töpper et al. (2003)	Saitoh et al. (2003)
1.a Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?	0	1	1	1	1	1	1	0	1	0
1.b The method was adequate?	It is not clear	1	It is not clear	It is not clear	It is not clear	1	1		–1	
2.a Was the study described as double blind?	1	1	0	1	1	0	1	1	0	0
2.b The method was adequate?	1	1		It is not clear	1		It is not clear	1		
3 Was there a description of withdrawals and dropouts?	1	0	0	0	0	0	1	0	0	1
Total score	3	4	1	2	3	2	4	2	0	1

Score: each item (1, 2, and 3) receives 1 point for yes or zero for no. An additional point is given if in item 1 the method of randomized sequence generation was described and was adequate, and in item 2, if the double-blind procedure was described properly. One point is removed if in question 1 the method of randomized sequence generation was not properly described, and in question 2, if it was described as double-blind but the description was inadequate.

through the SF-36 test, where the results were inconclusive due to a significant variability in the results. Belatedly, Kikkert and collaborators investigated in 2019 whether PLP relief was produced by the targeting of phantom hand representation. They used excitatory tDCS over the S1/M1 missing hand cortex and measured the neural underpinnings of PLP relief during and after tDCS with neuroimaging. A single NIBS intervention substantially eased PLP, with results lasting for at least 1 week. PLP was related to increased primary somatosensorial cortex (S1)/M1 activity and a positive correlation was found between PLP relief and decreased S1/M1 activity (Makin et al., 2015), further emphasizing the driving role of the mid- and posterior insula as well as the secondary somatosensorial cortex (S2) in PLP modulation (Kikkert et al., 2019).

Invasive treatments

Invasive neuromodulation is known to be the last option of treatment, and thus the use of these procedures is limited to patients who have failed multiple attempts at noninvasive treatments. DBS is conducted in subcortical areas following stereotactic implantation of thin stick leads. Evidence suggests that the significance of DBS is controversial for PLP (Knotkova et al., 2012). There is only one clinical trial involving DBS and PLP patients (Rasche et al., 2006) who have used DBS to treat different chronic pain syndromes that do not respond to conservative or less invasive methods of treatment. They included 56 patients with neuropathic or mixed nociceptive/neuropathic pain, 4 of whom had PLP. Electrodes were implanted in the somatosensory thalamus and the periventricular grey area. A double-blinded assessment was conducted prior to implantation of the stimulation system to assess the effect of each electrode on its own as well as the combined stimulation with various parameter settings. Of the four PLP patients, two of them obtained 25% to 100% pain relief, while the other two patients did not respond in any manner. Notwithstanding inconclusive results of this series, PLP as a main peripheral neuropathic pain with secondary central changes is considered a very good indicator in the literature for using this procedure due to well-circumscribed pain (Falowski, 2015).

MCS, which uses epidural surgical leads and subthreshold stimulation, is an electrical cortex stimulation. The use of MCS has traditionally been used in patients with post-stroke pain or neuropathic trigeminal pain (Rasche et al., 2006), whose results constitute an option for PLP patients. The only clinical trial testing MCS in PLP patients was conducted in 2003 (Saitoh et al., 2003), using MCS in 19 patients with intractable neurogenic pain of different origins, 2 of which were PLP patients. They tried to determine the best stimulation point for pain relief by putting the grid electrode in the subdural space, selecting the interhemispheric fissure, central sulcus and precentral gyrus. The 14 patients reported differing levels of pain tolerance and concluded that the ideal stimulation point for pain relief was Brodman region 4 within the central sulcus.

Limitations

The main limitation of our study, is that, based on the Jadad Scale for Reporting Randomized Controlled Trials, only four of the clinical trials included are rated as high-quality. Another limitation is that these trials involved a very small number of participants, with five participants in the smallest sample. Furthermore, most of the studies did not only study PLP syndrome. Other types of pain, such as post stroke or spinal cord injury were included, particularly in trials involving tDCS, DBS and MCS treatments, and hence conclusions should be taken with caution. Finally, because of the limited number of reviews of clinical trials, observational research may be considered to complete the overall literature review.

Conclusions

rTMS may be an effective treatment to minimize pain sensation in PLP, supporting pain scale findings and increasing serum beta-endorphin after treatment. Likewise, tDCS might also be an effective treatment approach even 3 or 4 weeks after a single treatment session. In the M1 network, PLP is associated with cortical excitability and nonpainful phantom experiences have been associated with hyperexcitation of PPC. Thus, increased anodal excitability of tDCS in M1 is associated with an antalgic effect on PLP; and cathodal tDCS stimulation on PPC is correlated with the enhancement of nonpainful sensations. Evidence in DBS to date indicates that the importance for PLP is controversial, however in the literature, PLP is considered to be a good indicator for the use of this treatment due to well-circumscribed pain. Certainly, MCS may be a choice for PLP patients due to the outcomes of this procedure in other forms of neuropathic pain. In this sense, Brodman area 4 within the central sulcus would be the optimum stimulation point for pain relief. In summary, noninvasive treatments to stimulate the central nervous system, such as rTMS and tDCS, may be beneficial to reduce pain sensation in PLP. Invasive treatments also need further investigation, as these treatments tend to have positive outcomes in both PLP and other forms of neuropathic pain.

Author contributions: *MAGP and PR developed the initial literature search strategy and performed eligibility screening, carried out the search and the data extraction and methodological quality assessment. When the consensus was not obtained, DC was consulted. MAGP assumed the main responsibility for the writing of the first draft of the manuscript. DC, LRR and PR contributed critically in the corrections until getting the final version that was approved for all the authors. All authors were involved in manuscript conception, design, writing, preparation, editing, review, and literature search, and discussed and carried out critical revisions for important intellectual content.*
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Peer review: *Externally peer reviewed.*

Open peer reviewer: *José M. Ferrandez, Universidad Politecnica de Cartagena, Spain.*

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