# Prevention and control of chronic post-amputation pain of extremities: systematic review

*Prevenção e controle da dor crônica pós-amputação de extremidades: revisão sistemática*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Post-amputation pain is very frequent and can become chronic in almost 85% of the cases. The objective of this study was to conduct a systematic review concerning the evidence about the measures for the control or remission of chronic pain in the stump or phantom limb in adults and the elderly after extremity amputation.

**CONTENTS**: The search was conducted in the databases Pubmed, Mendeley, Livivo, and Science Direct. Additional searches were performed at ClinicalTrial.gov, Google Scholar, and in the references of the selected articles. Two independent reviewers performed the screening of the studies as well as the data extraction and synthesis. The *Cochrane Collaboration Risk of Bias Tool* was used to analyze the risk of bias, and four articles were identified. Two articles on pharmacological prevention strategies and two articles on non-pharmacological treatment. The risk of bias was low for the pharmacological approach, and uncertain or high for the non-pharmacological.

**CONCLUSION**: The findings suggest a protective effect of preventive pharmacological therapies, epidurally, in combination with bupivacaine and fentanyl or added to calcitonin, in the perioperative period. Promising data are also presented for non-pharmacological therapies for pain control, phantom motor execution and gradual motor images. However, caution is necessary due to the risk of bias and considering the number of studies that answer the research question. Additional studies are suggested to strengthen the evidence, especially with quantitative analysis.

**Keywords**: Amputation, Perioperative period, Phantom limb, Postoperative pain, Therapeutics.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A dor pós-amputação tem alta prevalência, podendo tornar-se crônica em até 85% dos casos. O objetivo deste estudo foi analisar as evidências acerca de medidas para o controle ou remissão da dor crônica no coto ou membro fantasma em adultos e idosos com amputação de extremidades.

**CONTEÚDO**: Realizaram-se buscas nas bases Pubmed, *Mendeley*, Livivo e *Science Direct*. Buscas adicionais foram realizadas na página eletrônica *ClinicalTrial.gov*, *Google Scholar* e listas de referências dos artigos selecionados. A triagem dos estudos, bem como a extração e síntese dos dados, foi realizada por dois revisores independentes. A análise do risco de viés foi feita pela *Cochrane Collaboration Risk of Bias Tool*, sendo identificados quatro estudos. Dois sobre estratégias de prevenção farmacológica, e dois sobre estratégias de tratamento não farmacológico. O risco de viés foi baixo para as abordagens farmacológicas, e incerto ou alto para as abordagens não farmacológicas.

**CONCLUSÃO**: Os achados sugerem efeito protetor das terapias farmacológicas preventivas, por via peridural, em combinação de bupivacaína e fentanil ou somados à calcitonina, no período perioperatório. Dados promissores também são apresentados para as terapias não farmacológicas de controle da dor, execução motora fantasma e imagens motoras gradativas. Porém, é necessário prudência devido ao risco de viés e considerando a quantidade de estudos que respondem a pergunta de pesquisa. Sugerem-se estudos adicionais para fortalecer as evidências, especialmente com análise quantitativa.

**Descritores**: Amputação, Dor pós-operatória, Membro fantasma, Período perioperatório, Terapêutica.

## INTRODUCTION

Amputation is the removal of all or part of a limb. In Brazil, between 2008 and 2015, the Hospital Information System of the Unified Health System recorded 361,585 amputations, approximately 4,304 amputations per month[1]. In the United States, it is estimated that by 2050, approximately 1,6 million people will undergo this procedure[2]. Among the most common causes of amputation are trauma, diabetes mellitus, peripheral vascular diseases, and tumors[3-5].

Amputees are patients who have a high prevalence of post-surgical pain, about 70% have some type of pain that can be intense in up to 15% of the cases[4], and acute or chronic, depending on the duration. Post-amputation pain can be of two kinds, which

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many times coexist in the same patient: residual limb or stump pain (SP), and the phantom limb pain (PLP), a painful sensation in the surgically removed limb or part of it[5].

It is estimated that 50 to 85% of the amputees develop chronic post-amputation pain (CPAP)[6]. Four primary criteria are used to diagnose. Initial pain after the surgical procedure – however, on amputation, the presence of pain before surgery is not exclusionary, being a characteristic of the chronicity that after amputation the pain remains or even worsens; persistent for a variable period from two to six months or more; with the factors that have led to amputation no longer present in the individual, and not related to the natural course of the disease – as in the oncologic cases[5,7].

Since it is a potentially disabling condition, which pathophysiology is not fully understood, effective strategies to prevent and manage post-amputation pain are challenges to overcome as there is no consensus about the most effective and efficient way to address it[8].

The objective of this study was to gather evidence on the control or remission of the chronic stump or phantom limb pain in adults and the elderly with amputation of extremities.

## CONTENTS

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA checklist)[9] and the Synthesis Without Meta-analysis (SWiM) guideline[10]. The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO 2020 CRD42020151543). The question of the study was defined according to the PICO acronym[11]. "What is the evidence in the literature about measures to control chronic pain (stump or phantom limb) in adult and elderly patients with amputation of extremities"?

Clinical trials with preventive and/or therapeutic approach conducted with humans were included, with no language restriction, that addressed pharmacological and non-pharmacological interventions to prevent and manage post-amputation pain in adults or elderly patients, with outcomes of interest on chronic pain, stump pain and phantom pain, published between 2009 and 2019. Reviews, meta-analysis, case reports, and case series were excluded.

**Information source and search strategy**

The electronic databases Livivo, Mendeley, Pubmed and Science Direct were consulted on 08/07/2019. The search strategy was established according to the PICO strategy described above, adapted for each base ("amputation" OR "amputation stumps" OR "extremities amputation" OR "amputees" OR "limb amputation") AND ("Drug therapy" OR "non-pharmacological therapy" OR "pharmacological therapy") AND ("chronic pain" OR "Pain" OR "Pain, intractable" OR "Phantom limb") (Appendix 2). In addition, a search was performed in the records of the ClinicalTrial.gov website and in the gray literature (Google Scholar). The manual search in the reference lists of the selected articles did not show articles that could be analyzed within the scope of this study.

**Selection of the studies**

Two revisors read the titles and abstracts of the studies identified in the search. The studies that met the inclusion criteria were fully read and analyzed by the revisors. A third revisor solved the discrepancies in the selection, and those studies that did not meet the inclusion criteria were excluded.

**Process of data collection**

Two revisors collected the data independently with the general characteristics of the study including author, year, location, objective, design, characteristics of the therapy used – prevention or treatment, pharmacological or non-pharmacological, characteristics of the pain, intensity, site, type – SP or PLP, characteristics of the amputation, site of the surgical procedure, cause, and outcome with the respective results. A third revisor solved the discrepancies in the collection.

**Risk of Bias analysis**

The risk of bias of the studies included in the review was assessed by the Cochrane - Risk of Bias Tools (ROB)*[12]. It is a two-step assessment tool that assesses seven domains concerning the generation of the random sequence, blinding of participants and professionals, blinding of the outcome assessors, incomplete outcomes, report of the selective outcome, and other sources of bias. The first step assessed the existence of enough details to make a judgment based on the information provided. The second step judged the risk of bias of each of the domains that were then classified into three categories: low, high, or uncertain risk of bias[13,14].

**Summary of the measures and synthesis of the results**

The primary outcome was prevention, improvement, or total remission of CPAP, whether SP or PLP. The findings of the studies included were reported by the descriptive synthesis of the results.

The surveyed database identified 11,527 records. After removing the duplicates, 3,273 references went to the selection phase when the titles and abstracts were read. Eighteen documents were added from the reference list, exploratory search, and records on the ClinicalTrials.gov website. After reading the titles and abstracts, 35 studies were selected for full reading and eligibility assessment, of which 31 were excluded (Figure 1), and four studies made up the final sample. Figure 1 describes the process of identification, selection, eligibility, and inclusion of the studies.

**General characteristics of the studies**

The studies selected for review were published between 2011 and 2019, in English; two studies were conducted in Europe and two in Africa. Regarding the interventions for CPAP, two studies[15,16] reported pharmacological strategy for prevention, and two studies[17,18] reported a non-pharmacological strategy (Table 1).

Table 1 shows the data extracted. The studies were classified according to the applied intervention strategy – preventive or

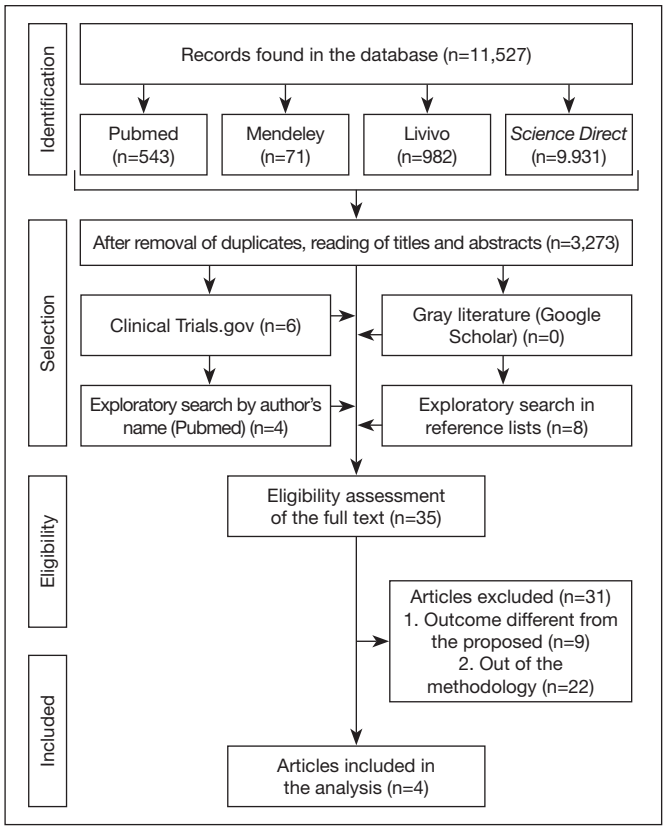


**Figure 1**. Flowchart of the search in the literature and selection process Brasília, DF, Brazil, 2019

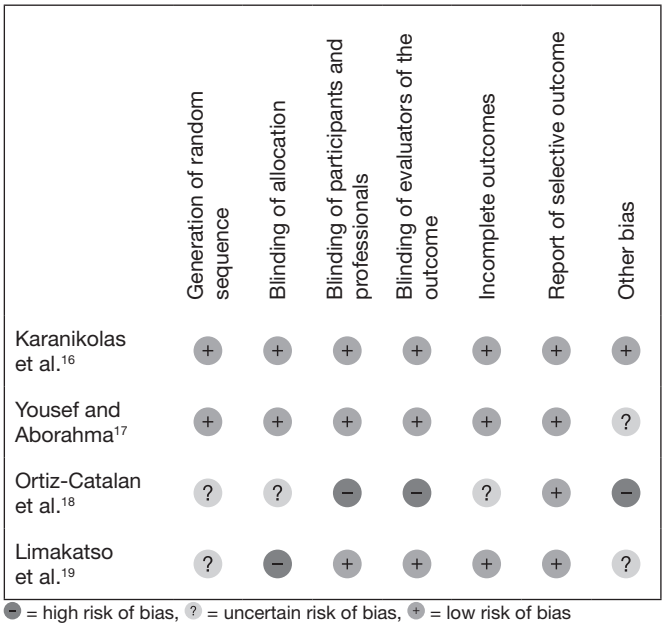


**Figure 2**. Assessment of the risk of bias of the studies included in the review. Brasília, DF, Brazil, 2019

treatment, and its modality – pharmacological or non-pharmacological, as well as the outcome. Amputation of lower and upper limbs was reported due to vascular disease, diabetes mellitus, trauma, infection, and tumor. All studies had, at least, a follow up of six months. All studies that assessed the strategies to treat and control CPAP analyzed patients who had been in pain for more than three months[17,18].

**Risk of individual bias of the studies**

The risk of bias analysis showed that 50% of the analyzed articles[15,16] had a low risk of bias in their conduction, being them of CPAP prevention and pharmacological therapy. One of the studies on non-pharmacological therapy was classified as a high risk of bias because it did not provide enough information on the randomness in sequence generation, allocation of subjects, and incomplete outcomes, and data that denied the blinding of participants/professionals and outcome evaluators[17]. Another study was classified as an uncertain risk of bias due to insufficient information on the random sequence generation process and to assess the existence of an important risk of bias[18] (Figure 2).

**Results of the individual studies**

One study[15] analyzed the impact of different pharmacological treatment regimens with a focus on the perioperative analgesia for the CPAP outcome, including SP and PLP in the lower limbs (LL). The considered perioperative period was 48h before and 48h after the amputation. Sixty-five patients were allocated in five groups (Table 1). The anesthesia varied among groups 1 to 4; epidural or general, and pre- and post-surgical analgesia with fentanyl, intravenous, and controlled by the patient, or epidural together with bupivacaine, continuous. Group 5, the control, received the standard treatment of the institution of the study (Table 1). The outcomes showed in table 1 refer to the analysis, six months after amputation. The outcome comparisons were among the treated groups and the control group (Table 1). Only group 1 - bupivacaine + epidural fentanyl (p=0.001) had a PLP intensity significantly different from the control.

Nevertheless, the prevalence of PLP was significantly different in the control group from groups 1, 2 and 4 (p=0.004) (Table 1). Given this data, and for the purpose of this review, it will be considered as a successful treatment, the one received by group 1. There was no difference in SP among the treated and the control groups.

Study[16] assessed the preventive role of calcitonin combined with bupivacaine and fentanyl epidurally for SP, analyzing hyperalgesia and allodynia, and PLP in amputations of the LL. The treatment was performed in the perioperative and every 24h, for two days after surgery. There was no preoperative treatment. Two groups were tested with 30 patients each. The control group received the same treatment protocol, with no calcitonin. Both SP and PLP were significantly lower in the group treated with calcitonin in combination (p=0.013 for allodynia and p=0.025 for hyperalgesia in SP, and p=0.001 for PLP). The prevalence of PLP was 100% in both groups.

Study[17] analyzed the effectiveness of the phantom motor execution with the aid of equipment to recognize myoelectrical patterns, using virtual reality, augmented reality, and gamification. The analysis compared the baseline values and the values after 12 intervention sessions. The amputations were of the upper limbs, and the individuals have had untreatable pain for an average of

**Table 1.** Summary of the descriptive characteristics of the studies included in the review (n=4). Brasília, Distrito Federal, Brazil, 2019

| Authors | Objectives | Samples (n) / follow-up | Type and cause of amputation | Therapeutic strategy | Therapeutic modality | CPAP outcome |
|---|---|---|---|---|---|---|
| Karanikolas et al.[15] | Assess the hypothesis to optimize the perioperative analgesia using continuous epidural analgesia or intravenous PCA to reduce the intensity, prevalence, and frequency of the phantom and/or residual pain after the elective amputation of LL. | 65/6 months | LL amputation due to peripheral vascular disease. | Prevention. Interventions performed in the perioperative, 48h before and 48h after the procedure, continuously. | Pharmacological<br>Group 1: continuous epidural analgesia in the perioperative (bupivacaine and fentanyl. Epidural anesthesia (bupivacaine and fentanyl.<br>Group 2: preoperative analgesia with PCA intravenous fentanyl; in the peri and post-operative; continuous epidural analgesia (bupivacaine and fentanyl). Same anesthesia as group 1.<br>Group 3: pre- and post-operative analgesia with PCA intravenous fentanyl; in the peri and post-operative; continuous epidural analgesia (bupivacaine and fentanyl). Same anesthesia as group 1.<br>Group 4: pre- and post-operative analgesia with PCA intravenous fentanyl. General anesthesia.<br>Group 5: Control pre- and post-operative analgesia with intramuscular meperidine plus oral codeine/paracetamol. Additional analgesia with paracetamol plus parecoxib, intravenous, if necessary. General anesthesia. | Group 1 had a significant reduction in PLP intensity.<br>Prevalence of PLP:<br>- Group 1: 7.7%<br>- Group 2: 30.7%<br>- Group 3: 58.3%<br>- Group 4: 23%;<br>- Group 5: 75%.<br>There was no difference in SP. |
| Yousef and Aborahma[16] | Assess the preventive role of epidural calcitonin on post-surgical pain, chronic phantom pain degree, and development of hyperalgesia and allodynia in patients who have undergone amputation of the LL with combined spinal anesthesia. | 60/12 months | LL amputation due to peripheral vascular disease in diabetic patients. | Prevention Interventions performed in the perioperative (anesthesia) and at every 24h after the surgery for two days after the procedure. | Pharmacological<br>Group 1: epidural bupivacaine + calcitonin + fentanyl<br>Group 2: epidural bupivacaine + fentanyl | The PLP intensity was significantly lower in group 1 patients.<br>100% PLP prevalence in both groups.<br>SP hyperalgesia and allodynia were significantly less frequent in group 1 patients. |
| Ortiz-Catalan et al.[17] | Examine the effectiveness of PLP therapy based on phantom motor execution. | 14 / 6 months | Amputation of UL due to trauma (12 subjects), tumor (1 subject), or infection (1 subject). | Treatment Sessions with individuals with non-responsive PLP to conventional treatment and average duration of 10.3 years. | Non-pharmacological<br>Twelve sessions of phantom motor execution upon the recognition of myoelectrical patterns, using virtual reality, augmented reality, and game. | Significant PLP reduction. |
| Limakatso et al.[18] | Investigate if the graded motor imagery is effective in reducing PLP. | 21/6 months | Amputation of upper or LL due to complications from diabetes mellitus (16 subjects), trauma (3 subjects), and infection (2 subjects). | Treatment Intervention program with individuals with self-reported PLP, persistent for 3 months or more. | Non-pharmacological<br>Six-week intervention<br>Group 1: graded motor imagery therapy<br>Group 2: control, conventional physiotherapy. | The reduction in PLP intensity in group 1 was significantly different from the control group. |

CPAP - chronic post-amputation pain; SP = stump pain; PLP = phantom limb pain; PCA = patient-controlled analgesia; LL = lower limbs; UL = upper limbs.

10.3 years. There was a significant improvement in PLP, with a 47% reduction (p=0.001) (Table 1).
Study[18] investigated the effectiveness of a 6-week program of graded motor imagery treatment for PLP in subjects mostly with LL amputation, divided into intervention group and conventional physiotherapy control group. The group that received the intervention showed a significant reduction in PLP when compared with the control (p=0.03). In addition, the data analysis allowed to deduce that the individuals who received the intervention would have 15 times more chance to have a significant reduction in PLP than those of the control group.
It is worth noting that a meta-analysis was not conducted in this review, due to the number of studies eligible for analysis and their heterogeneous characteristics.

**Summary of the results**
All the studies included had results significantly different from the control groups[15,16,18] or the patients' baseline[17]. In summary, the pharmacological treatment to control pain in perioperative prevents CPAP (SP and/or PLP), showing promising results both for intensity and prevalence. However, there are still some questions that suggest the need for additional studies: 1) a regime that includes pre-surgical treatment seems to have an impact on the prevalence and intensity of PLP, reducing them[15], 2) a regime that includes epidural calcitonin seems to have an impact on the SP frequency and PLP intensity, but not on its prevalence[16]. The pharmacological treatment involving the phantom motor execution[17] or graded motor imagery[18], controls PLP, reducing its intensity. These questions still remain for these approaches: 1) it was not possible to establish the impact of these treatments for SP since it has not been addressed in the studies; 2) additional studies with a lower risk of bias may be useful for establishing more robust evidence.

## DISCUSSION

Four studies met the inclusion and exclusion criteria and were grouped into subgroups according to the therapeutic strategy – prevention or treatment, and approach – if pharmacological or non-pharmacological. Pharmacological approaches were used for the prevention of CPAP, analyzing the PLP and SP outcomes. Non-pharmacological approaches were used for the treatment of CPAP, analyzing the outcomes for PLP, not mentioning SP. Despite the differences in the observed effects, the risk of bias in some studies, and the clear need for additional studies, all proposed approaches showed statistically significant benefits to the CPAP primary outcome, whether for prevention or control.
When prevention and acute pain treatment measures are applied, the incidence, prevalence, and intensity of chronic pain can be substantially minimized. In this sense, the peri, pre, intra, and post-operative multimodal pharmacological analgesia is among the most effective measures described in the literature, with the epidural use standing out for the control of the amputation-related pain[5,19-22].
In this study, it was found that the pharmacological treatment of continuous perioperative analgesia with a bolus dose of bupivacaine, fentanyl plus calcitonin, both epidurally, prevented the development of PLP in a significant number of subjects[15], and those who have developed it, the pain intensity was lower[15,16]. The protocol that used calcitonin showed significant results in reducing the frequency of SP[16].
For the treatment of pain, in general, there is evidence of the efficacy and benefits of the drugs and the epidural administration used in the studies analyzed in this review. Bupivacaine blocks the voltage-gated sodium channels, stabilizes the neural membrane, and decreases the nerve impulses. Depending on the dose, it can have a local anesthetic or analgesic effect. It can be used during the entire perioperative period and in the treatment of chronic pain[23,24]. The epidural route is well-established as safe and effective, and also providing synergetic effects with opioids, including fentanyl, also epidurally[24]. Fentanyl is a synthetic opioid, μ-receptor agonist with fast and intense initial analgesic effect, but of short duration. The association of local anesthetics with opioids epidurally has been described as a promoter of better-quality analgesia when compared to its single use, whether epidurally or systemic route in the case of opioids[23]. Calcitonin is a hormone produced by the thyroid gland cells, responsible for regulating the calcium homeostasis. Its effect in controlling pain has been reported for different types of neuropathic pain, including PLP[25-27].
The prevalence of PLP observed in the studies[15,16] was remarkably different; in the first, it was less than 10%, and in the second, 100%. In both studies, the cause of amputation was a peripheral vascular disease; however, the second study mentions that all patients had diabetes, which may have contributed to a higher prevalence of PLP since many could have a history of fiber sensory neuropathy. From the perspective of pain control, it is relevant that the first study had preoperative analgesia and that the entire analgesic regime was continuous. In the second study, analgesia was intra and post-operative in a bolus. The data analysis suggests the importance of considering the preoperative analgesia – 48h before the procedure, besides the intra- and post-operative analgesia – since it seems to impact the prevalence of PLP. This observation can guide future studies and can also be considered for the elaboration of clinical procedures.
Concerning non-pharmacological approaches, interventions based on the phantom motor execution and graded motor imagery showed significant results for the treatment of PLP; however, no data was presented for SP, and the analysis showed a risk of bias in the studies[17,18].
The motor execution for the phantom limb proposed in study[17] was carried out with the aid of a virtual and augmented reality equipment. The patient is placed in front of a screen, and the camera captures and transmits the actual image to the screen plus the virtual image of the amputated limb. From the recognition of the myoelectric patters of the stump through electrodes, the system predicts and projects the image of the phantom limb in motion. During the sessions, the patients performed movements with different difficulty degrees and played a game where the phantom limb drove a car. This therapy is independent of the contralateral side and can be especially useful for individuals with bilateral amputation. The need for recognizing the myoe-

lectric patterns requires that the patient has a controllable portion of the biceps and triceps, and this is a limitation.

TIMG used several motor imaging strategies, including: right / left trials where members representing patients' amputated limbs were shown and individuals were asked to imagine themselves performing the movements that the image was supposed to be performing; and mirror therapy, in which the patient positioned the stump of the amputated limb behind a mirror and the intact limb reflects his image in the same mirror[18].

Maladaptive mechanisms of the central nervous system plasticity, especially the somatosensory and motor cortex, and reduction of the inter-hemispheres connections are closely related with CPAP and PLP[20,21,28-30]. Although the mechanisms involved n the phantom motor execution, mirror therapy, motor imagery, and graded motor imagery still need to be better understood, they are certainly based on usual phenomena of the brain plasticity[17,31]. Some advantages of these approaches are the relatively low number of undesirable effects – although the transient exacerbation of PLP can occur during the treatment, the low cost, and the patient's independence to perform the exercises in some of them.

Although some patients were also on the pharmacological therapy during the protocols, the benefits of these combined therapies were not investigated, leaving another question for future studies.

CPAP is a complex condition, which mechanisms still require a better understanding. Although SP and PLP are different, especially in terms of sensory alterations clinically detectable by the patient's report and the sensory test of the stump, the pathophysiological mechanisms overlap. The point in common seems to be the afferent hyperexcitability before, during, and after amputation, leading to plastic alteration and reorganization of the peripheral afferents, and also the dorsal root ganglia, spinal dorsal horn, brain stem, thalamus, and cortical structures, as well as the sympathetic activation[6,20,30]. Therefore, the benefits found in this review, both for the pharmacological and non-pharmacological treatments, which mechanisms were addressed above, can be ultimately explained by the action in different levels of the organization of the sensory pathways, preventing or reverting the alterations in response to amputation. Following this line of thought, the pharmacological approaches that promote the reduction in peripheral and spinal excitability in the perioperative period have the benefit to prevent such alterations and reorganization of the sensory system in the maladaptive sense. The therapies to treat PLP analyzed in this review have a known impact on the cortical reorganization that occurred due to amputation, contributing to its reversion.

## STUDY LIMITATIONS

Amputation is a situation of high vulnerability to individuals. In addition, some of the procedures are carried in urgent or emergency situations. The combination of these facts contributes to making it difficult to perform and conduct studies, influencing the sample size, randomization, blinding, outcome measures, and other variables that impact the higher risk of bias found in half of the studies of this review.

For review purposes, the sample of this study is a limitation. The time established for the search may have influenced since there are studies in the reference lists found in the exploratory search that are cited in the literature and are previous to the established timeframe, especially after the nineties, suggesting its importance and shortage of studies. The methodology of the studies may also have impacted since 22 articles were excluded because they did not meet the inclusion criteria for being a case study or case series. Another limitation was that no studies on CPAP were found, whether pharmacological with gabapentin, pregabalin, anticonvulsants, memantine, and NMDA agonists[23], or non-pharmacological such as transcutaneous electrical nerve stimulation, vibration therapy, acupuncture, hypnosis, biofeedback, electroconvulsive therapy, cognitive-behavioral approach, physiotherapy, manipulation, ultrasound, repetitive transcranial magnetic stimulation, spinal stimulation, and cryoneurolysis[22,23,32,33].

## CONCLUSION

From the analysis of the studies included in this review, it is possible to suggest a protective effect of preventive pharmacological therapies for CPAP, administered epidurally, in combination with bupivacaine and fentanyl or the first two added to calcitonin, in the perioperative regime. Although the risk of individual bias in the studies was low, further studies are recommended in order to strengthen the evidence. For non-pharmacological therapies to control CPAP, phantom motor execution and gradual motor images, although there are promising data with the prospect of positively impacting the lives of individuals, greater caution is necessary in view of the risk of uncertain bias and high risk of observed bias. Although the set of data presented is promising, caution is necessary since it was not possible to quantitatively analyze the findings of this review. The data presented in this study can be useful to assist in the establishment or reinforce conducts already adopted in care protocols and in the conduct of new studies responding to the gaps that remain.

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