

Research Article

A Study on Relationship among Phantom Limb Pain

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Abstract: Various phantom limb phenomena were researched using 32 unilaterally amputated upper extremity patients, some of whom experienced phantom limb pain and some of whom did not. In general, individuals who suffered from phantom limb had a greater incidence of non-full phantom limb sensations than amputees who did not experience any from their amputations. Exteroceptive cutaneous sensations were reported less frequently than kinesthetic and kinetic phantom limb experiences, which were reported more frequently. Phantom limb and stump were found to have a substantial and positive link with one another. Patients typically attributed sensory rather than affective characteristics to their phantom limb, however for stump; no differences were identified between qualities.

Keywords: Phantom Limb Pain, patient, stump.

Introduction

After having a limb amputated, some patients continue to endure pain in the portion of the limb that has been removed. Phantom limb is the term used to describe this phenomenon. The suffering is really genuine. The missing limb or portion of the limb is referred to as the "phantom part," and it is the site of the pain¹.

Phantom limb (PLP) is that is "localized in the location of the removed body part," according to the definition of the term. Due to the acute and chronic character of the syndrome, it is a clinical phenomenon that is still the focus of much research despite the fact that it is poorly understood. It has been observed that the incidence is as high as 60-80 percent in patients who have undergone amputation, and risk factors include persistent in the period leading up to the amputation, post-operative surgical, and emotional anguish^{2,3}.

- ✓ Phantoms are frequently characterized as sensations such as crushing, toes twisting, hot iron, scorching, tingling, cramping, startling, shooting, and "pins and needles."
- ✓ Has a propensity to concentrate in more remote phantom structures (e.g. fingers and toes)
- ✓ Prevalence in the early stages ranges from sixty to eighty percent
- ✓ Unaffected by the patient's age, gender, amputation degree, or side of amputation in adults

Phantom sensation is a separate phenomenon from phantom limb that can affect people who have had a limb amputated. Phantom sensation is quite common and has been shown to have no correlation with complaints of Phantom experiences can be broken down into the following categories:

- ✓ Kinetic (movement)
- ✓ The kinesthetic sense (size, shape, position)

✓ Exteroceptive (touch, pressure, temperature, itch, vibration)

Ambrose Pare, a French military physician working in the sixteenth century, is credited with being the first person to define the idea of phantom limb (PLP). PLP is the perception of in a part of the body that is no longer physically there.

The phrase "phantom limb" was developed by the well-known Civil War physician Silas Weir Mitchell, who also offered a full description of this ailment⁴, Mitchell worked throughout the nineteenth century during the American Civil War.

It is still a medical issue that is tough to understand as well as treat, and this has not changed. According to the findings of a recent research, the number of persons living in the United States who had lost a limb in 2005 was around 1.6 million, and it was expected that this figure would more than double to 3.6 million by the year 2050⁵.

Some of the most prevalent factors that lead to limb amputation are vascular issues, trauma, cancer, and congenital limb deficiencies. Since the commencement of the conflicts in Iraq and Afghanistan, there has also been a rise in the frequency of amputations caused by trauma⁶.

In patients who need to have a limb amputated, the incidence of PLP has been observed to range anywhere from 42.2% to 78.8% of the time. Phantom sensations, on the other hand, are experience sensations in a body part that no longer exists^{7,8}. Stump is the term used to describe the piece of the severed leg that is still there.

Touch and pressure-like sensations can be felt on the phantom limb from things such as clothes⁹, and these sensations are referred to as superadded phantom sensations. Recent studies have shown that the prevalence of PLP is higher among amputees of the upper limbs than it is among amputees of the lower limbs. In addition to this, it was observed to be more prevalent in girls than in males^{10,11}. According to the findings of a survey, females experience higher levels of overall average intensity and interference than males do. Additionally, females report significantly higher levels of catastrophizing, using certain-coping strategies, and holding beliefs related to multiple aspects, which results in poor adjustment¹².

For a more definitive establishing of the risks associated with PLP development according to the location of the injured limb or the gender of the patient, larger population studies are need to be conducted. Phantom sensations and have been reported following amputation of various body parts, such as the eyes, teeth, tongue, nose, breast, penis, bowel, and bladder; however, the most common occurrence is following limb amputation. Phantom sensations and have been reported following amputation of the limbs. Phantom and sensation might begin as soon as the amputated limb is removed, or they can develop several years afterwards. There have been reports of two peak times of onset, the first occurring within a month following amputation and the second occurring a year later. It has been claimed that the prevalence would diminish over time following the amputation. PLP has been reported in patients who were born without limbs due to a congenital defect¹³. Some of the most often cited forms of are tingling, throbbing, piercing, and pins and needles sensations.

It has not been observed that those who have had both of their limbs amputated are more likely to experience phantom or sensation than those who have just had one of their limbs amputated¹⁴. The PLP has been shown to have a substantial connection with residual limb, according to research published in¹⁵. It has also been reported that having preamputation raises the risk of developing post-amputation syndrome¹⁶. It is quite likely that factors such as stress, anxiety, sadness, and other emotional triggers are contributors to the continuation of or an escalation of PLP. According to the findings of one research¹⁷, amputees who had depressed symptoms were more likely to describe the severity of their as being higher than those who did not experience any depression symptoms.

Methodology

A non-systematic evaluation of the research published in PubMed and Cochrane was carried out, and the following terms were introduced through the use of key words: pathophysiology, phantom limb, and neuropathy. We went over some of the most important pieces and spoke about them.

Results and Discussion

Pathophysiology of PLP

PLP might last for a very brief period of time and is accompanied by excruciating cramps, or it can be ongoing and be accompanied with a heightened awareness of the absent limb can have a shooting, throbbing, searing, or cramp-like quality pain, and it is typically more acute in the more distal areas of the body. It is possible for it to manifest either immediately or many years after the amputation was performed. According to the findings of prospective research, fifty percent of patients may suffer pain during the first twenty-four hours following an amputation, and sixty to seventy percent may do so one year later. Even while it happens more frequently after amputation of a limb, it is possible for it to happen after the surgical removal of any portion of the body, including the eyes, breasts, face, and so on^{18,19}.

Although there is little information to draw conclusive conclusions, it is possible that the onset and type of PLP will vary depending on the reason why the amputation was performed. Diabetes mellitus and chronic vascular disease are the most common reasons for amputation in western nations; tumors are a less common cause of amputation. Diabetes is the most common cause of amputation in western countries. In some regions of the world, civil conflicts and land mines are two of the most common factors that lead to traumatic amputations in otherwise healthy people.

Circumstantial considerations

After nerve sectioning, there is retrograde degeneration and shortening of afferent neurons due to the damage, edema, and axon regrowth that occurred as a result of the procedure. This process, which is known as sprouting, is what leads to the production of neuromas, which are characterized by enlarged and disordered A and C fibre ends that exhibit ectopic firing and become more active in response to mechanical and chemical stimuli. Ibers of the type C are distinguished by the expression of an ectopic discharge that has a slow, irregular pattern. This is associated with an up-regulation or "de novo" expression of sodium channels, and a down-regulation of the potassium channels. In addition to this, there is an alteration of the transduction molecules for mechano-sensitivity signals. The fact that local anaesthetic of the stump does not eradicate in all situations is a good illustration of the points made above. Additionally, the injection of gallamine, which is a chemical that increases sodium conductance, results in phantom^{5,6}. It's possible that aberrant spontaneous activity is also caused by the link between axons that isn't working properly. However, PLP can appear in certain individuals shortly after an amputation and even before the formation of a neuroma. Because of this, the latter mechanism cannot adequately explain the pathophysiology of PLP⁹.

The dorsal root ganglion (DRG) is another location where ectopic discharge can occur. The DRG joins the ectopic activity that is produced by the stump neuroma and either amplifies it or creates crossing excitation, both of which result in the depolarization of the neurons that are located nearby. It has been demonstrated that the use of beta-adrenergic blockers or the surgical inhibition of sympathetic activity can alleviate, whereas epinephrine injections can cause an increase in the intensity of the pain that patient experience. In addition, the pathophysiology of this condition is significantly impacted by a number of environmental variables, including temperature, oxygenation, and local inflammation that occurs over the neuromas or the DRG²⁰.

The most important factors

The malleability of the spine

There is evidence of central sensitization of the neurons in the posterior horn of the spinal cord after damage to the peripheral nerves. This mechanism is characterized by long-term potentiation, which

is when short-lasting nociceptive stimuli create enhanced post-synaptic potentials over a lengthy period of time^{14,15}. In addition to this, hyperexcitability, a downregulation of inhibitory processes, structural alterations in the primary central sensory nerve terminals, interneurons, and neuronal projections are all present¹⁶. The rapid firing from injured tissues and other effects of axotomy may be responsible for the destruction of gabaergic and glycinergic interneurons in the spinal cord. Alternatively, these interneurons may switch from inhibitory to excitatory activity under the influence of brain-derived neurotrophic factor (BDNF), thereby contributing to hyperexcitability^{4,6}. In addition, there is a reduction in the number of opioid receptors found on primary afferent terminals as well as intrinsic spinal neurons. Cholecystokinin, an endogenous opioid receptor inhibitor, has its production increased as a consequence of this, which makes the disinhibitory impact even stronger^{4,17,18}. Another mechanism that might explain sensitization is the inflammation-induced stimulation of glutamate NMDA (N-methyl-D-aspartate) receptors^{4,11}.

Injury to a nerve also results in the establishment of a functional link between low threshold inputs and ascending spinal projection neurons. These neurons are responsible for relaying nociceptive information to supraspinal regions. Substance P, which is generally generated by type A and type C fibres, is released by A mechanoreceptor fibres that function as nociceptive when they are injured, which is an extra mechanism that is triggered by the damage. It is possible that as a result of this, either ectopic or normal activity in the A fibres will be able to initiate or sustain central sensitization. When this occurs, a normal and innocuous input from the A fibres, an ectopic afference, and residual low threshold afferences may all contribute to the phantom sensation^{4,15}. In a similar fashion, there is a degradation of C fibres in lamina II, which allows space for the formation of A fibres across this region (ending normally in laminae III and IV). This leads second order neurons in lamina II, which typically receive high threshold sensory signals, to begin to receive low threshold signals. This gives rise to the impression of tactile stimuli as being nociceptive and induces allodynia in the patient^{4,9,15}. On the other hand, altered sensory and motor responses have also been proposed as a possible explanation. This theory is based on the assumption that the abnormal full sensation might be associated with a disconnect between the motor intention and the sensory response that is brought on by the activation of frontal and parietal areas in the brain.

Cortical reorganization

Experiments have shown that when an adult monkey has a digit amputated, there is an invasion of neuronal areas adjacent to the cortical area where the amputated digit was represented. This invasion is consistent with neuroplasticity changes that occur in the primary motor cortex (M1) and the primary somatosensory cortex (S1). Similarly, Ramachandran and colleagues observed a reorganization of Penfield's humunculus by approximately 2-3 cm in four amputees with phantom sensations in the amputated limb. There was a correspondence between stimulus sites in the face and phantom sensations in the amputated limb, which suggests that cortical reorganization may be the source of this phantom phenomenon. The phantom sensation in severed arms may be triggered from distant parts of the arm representation in S1, such as the toe, although it has been postulated that other regions of the brain may also be engaged in this process^{21,4}. It has also been reported that the intensity of the PLP increases in direct proportion to the degree to which the mouth representation has moved toward the anterior region of the arm. This finding suggests that topographic reassignment shifts over the course of time⁶. Even though they do not appear to be a component of the etiology, psychological variables have the potential to alter the progression and intensity of pain. It is possible that remodeling takes place not just in areas that are sensitive to sensory but also in areas that are sensitive to emotional such as the insula, the anterior cingulate gyrus, and the frontal cortex^{6,22,12}.

Methods of Treating PLP

As of right now, there is no clear consensus on the efficacy of the PLP therapy. This is due to the fact that less than 10% of patients who receive medical treatment experience long-term relief¹⁹⁻²¹. Both non-pharmacological and pharmaceutical approaches to treatment may be utilised^{21,5}.

Pharmacological therapy

Opioids

Opioids create analgesia by binding to opioid receptors in the central nervous system as well as in the peripheral nervous system. This process does not result in a loss of touch, proprioception, or consciousness.

The researchers¹⁷ conducted a cross-over double-blind study in which 12 patients with chronic PLP that was unresponsive to medical management and had an intensity of more than 3/10 on the Visual Analog Scale (VAS) were randomly assigned to receive oral morphine (with a maximum dose of 300mg/day) or a placebo. The patients were also required to have an intensity of more than 3/10 on the VAS. Their findings demonstrated a significant decrease in the amount of experienced during treatment with oral morphine, in comparison to the level of experienced during treatment with placebo ($t = -1.99$, $p = 0.036$), whereas there was no significant decrease in the amount of experienced by this latter group in comparison to the baseline level ($t = 2.18$, $p = 0.026$). More over half of the patients who were given oral morphine saw a reduction in their level of that was greater than 50 percent ($p < 0.05$). In the same manner, Study conducted a cross-over, randomized, double-blind, placebo-controlled trial in which 32 participants with chronic PLP and stump were evaluated to assess the efficacy of intravenous (IV) morphine. They demonstrated a statistically significant reduction in after 30 minutes after finishing the infusion, in comparison to the placebo ($p < 0.01$) (VAS score of 48 before the infusion and of 30 after the infusion).

The number needed to treat (NNT) for morphine administered intravenously to reduce by 30% was 2⁴. Later, Other study conducted randomized 60 subjects with post-amputation chronic (stump and PLP) greater than 3/10 on the VAS to administration of oral morphine, mexiletine, or placebo. They discovered a mean change in intensity in relation to the baseline level (-1.4 for placebo, -1.5 for mexiletine, and -2.8 for morphine, ($p < 0.0001$), with morphine providing the greatest reduction in intensity. Oral morphine demonstrated a statistically significant greater reduction in compared to both placebo and mexiletine ($p = < 0.0003$).

The number needed to treat (NNT) required to achieve a reduction of 33 percent with oral morphine was 4.5, while the NNT required to achieve a reduction of 50 percent was 5.6. Baron et al.²³ conducted a research in which they compared the efficacy of oral dextromethorphan (120 or 180 mg/day) to a placebo over a period of three weeks in three patients who had PLP as a result of amputation caused by tumour. This study was a cross-over, double-blind investigation. They discovered that the average level on the VAS before therapy in all three patients was between 8.5 and 10, and that this score decreased to between 2.8 and 7.1 ($p < 0.05$) after the patients had received treatment for three weeks with 120 mg of dextromethorphan.

Antagonists of the NMDA receptor

In a research that was controlled by a placebo and conducted with double blinding, MacIver et al.²⁴ randomly assigned 36 patients with chronic PLP to receive either 30 mg of memantine per day or a placebo. At the end of the study period of four weeks, the Numerical Classification Scale revealed that both groups saw a reduction in levels of (NCS). In the group that received memantine, the score decreased from 5.1 (2.13) to 3.8 (2.3), but in the group that received a placebo, the score decreased from 5.2 (2.02) to 3.2 (1.46) ($p < 0.05$). In addition, the mean improvement was comparable across the two groups (47 percent against 40 percent, respectively), and the number needed to treat (NNT) was 4.5.

Similarly, Roux et al.²⁵ carried out a study in which participants with chronic PLP were randomly assigned to receive either up to a maximum dose of 30 mg of memantine per day or a placebo for a period of three weeks. This trial was a double-blind, placebo-controlled investigation. On days 1 and 21 of therapy, Trans cranial magnetic stimulation (TMS) was used to measure the levels of intra-

cortical inhibition (ICI) and intra-cortical facilitation (ICF). The average score at baseline on the NCS for the memantine group was 4.1 (ranging from 1.7 to 6.3), whereas the score for the placebo group was 6.8 (ranging from 0.3 to 7.7). After three weeks of treatment, there was a significant increase in ICI ($p < 0.05$) in the group that received memantine (the average change in ICI in the placebo group was -0.3 percent, -13 percent, and -22.0 percent, while the average change in ICI in the memantine group was -25.5 percent, -42 percent to +7.0 percent). Similarly, the IFC decreased significantly ($p < 0.05$) in the group that received memantine (an average of -1.5 percent, with a range of -57.0 to +51.0 percent in the placebo group, vs -37.7 percent, with a range of -131.0 to +19.0 percent in the group that received memantine). There was not a significant difference in the mean decrease of phantom that was seen between the two groups (the placebo group saw a reduction of 0.9, with a range of -3.2 to +1.2, while the memantine group had a reduction of 2.5, with a range of -6.3 to +0.3).

Mechanisms that are mediated by memantine may have a significant influence on the increase in ICI and the reduction in IFC that occurs over the region of the brain that is contralateral to the amputation. In spite of this, the findings imply that the alterations in cortical excitability and PLP are not dependent on one another. Similarly, Berger et al.²⁶ conducted a randomized cross-over, double-blind, placebo-controlled study in 8 patients with chronic PLP. They discovered that there were no significant changes in the mean intensity measured on the VAS between the baseline level and after four weeks of treatment with 30 mg daily of memantine or placebo, or between the two treatments (the mean baseline between the two groups was 40, and after 4 weeks it was 42 with memantine and 43 with placebo. In the course of their therapy with memantine, five patients reported a somewhat elevated level of (mean at baseline: 46.98 20.38; with memantine: 51.51 20.61). In a trial that was randomized, double-blind, and cross-over, Eichenberger et al.²⁷ examined the effects of ketamine intravenously (i.e.) with calcitonin, ketamine + calcitonin, and a placebo in 20 patients who had chronic PLP that was more than 3/11 on the VAS. The percent change in immediately after completing the treatments showed that calcitonin was no different than the placebo, while ketamine alone and in combination resulted in a significant reduction of on the VAS, compared to placebo and calcitonin ($p < 0.05$). This was determined by looking at the percentage change in immediately after the treatments were finished.

Anticonvulsants

The analgesic action of gabapentin is caused by the drug's binding to the $\alpha_2\delta$ subunits of the voltage-dependent calcium channels found in the neurons of the posterior horn⁹. Gabapentin was evaluated in a randomized, double-blind, cross-over, placebo-controlled research with 19 patients (mean age: 55) who had chronic PLP with a VAS score of higher than 4/10. The study was carried out²⁸. After administering a maximum dose of 2.4 g of gabapentin per day for six weeks, followed by one week with no treatment, the researchers found that the mean difference in intensity on the VAS in the gabapentin group was significantly greater than in the placebo group at the end of treatment (3.2 2.1 versus 1.6 0.7, $p = 0.03$). This finding suggests that gabapentin is more effective than placebo in treating chronic. A randomized, double-blind, placebo-controlled, cross-over research was carried out by Hanley et al.¹⁶ on 24 participants who suffered from chronic PLP and had an intensity that was more than 3/10 on the NCS. These participants were given 3.6 g of gabapentin per day. No significant differences in score changes before and after therapy were identified at the conclusion of treatment in either group (0.94 1.98 versus 0.49 2.20 for placebo, $p = 0.70$).

The joint analysis of the results of the two most recent studies for the change in intensity with respect to placebo showed a mean difference in favor of gabapentin of -1.16 (95 percent confidence interval [CI], -1.94 to -0.38, $p = 0.004$). On the other hand, despite the fact that carbamazepine has been utilized in the therapy of neurogenic, only one case has been documented in PLP, and the findings were negative¹⁹. Only a few cases of pregabalin-induced peripheral lipidosis (PLP) have been described, despite the fact that pregabalin is indicated as a first-line treatment for the therapy of neuropathic. Although they have been shown to be successful in a few case reports, there is no solid

evidence to support the use of other anticonvulsants such as topiramate, lamotrigine, or oxcarbazepine at this time. Additionally, phenytoin, the first anticonvulsant used as anti-nociceptive has not demonstrated consistent effect of lowering neuropathic²⁹.

Antidepressants

The most frequent type of antidepressant prescribed is a tricyclic. They do this via inhibiting monoamine reuptake as well as calcium and sodium channels, which is how they moderate. Additionally, they block the NMDA receptor. Dickinson et al.³⁰ examined amitriptyline 125 mg daily vs benztropine mesylate in 39 participants with persistent phantom, and observed no significant changes between the two groups on the NCS (3.1 ± 2.7 for amitriptyline versus 3.1 ± 2.9 for benztropine, $p < 0.05$) after 6 weeks of therapy. A similar study concluded that the antidepressant amitriptyline is ineffective in the treatment of postpartum depression (PLP). Antidepressants like duloxetine, venlafaxine, chlorimipramine, and nortriptyline have only been investigated in isolated case studies.

Calcitonin

There is still a lot of mystery around the exact workings of calcitonin in PLP. In their study, Goodchild et al.³¹ looked at the effects of calcitonin against a placebo on 21 patients who were experiencing severe PLP between 0 and 7 days following amputation. When the score on the Numerical Analog Scale (NAS) was higher than 3, a first infusion of calcitonin or a placebo was given; if the remained, the infusion was given a second time (cross-over). It made no difference whether the first infusion was calcitonin or a placebo; after 24 hours of receiving 200 IU of calcitonin, the average score dropped from 7 to 4, and the difference was statistically significant ($p < 0.001$). It was discovered that there were no shifts in the level of (mean of 7 on the NAS, $p > 0.1$). At 48 hours after receiving a comparable dose of the drug, Eichenberger et al.²⁸ evaluated the patient's level of using the VAS and observed no improvement. In these two investigations, there was no significant difference between the placebo group and the active treatment group in terms of the proportion of patients reporting an improvement of more than fifty percent. These seemingly contradictory findings might be resolved by considering the possibility that calcitonin has no effect on the central sensitization that occurs in chronic PLP.

Anesthetics

In a double-blind, placebo-controlled, cross-over study, Casale et al.³² evaluated the effects of myofascial injections contralateral to the area of in 8 patients with chronic PLP. They found no significant differences in either group after the first (7.6 ± 1 versus 7.7 ± 0.6 on the VAS, $p = 0.9$) or the second (8 ± 1 versus 7.6 ± 0.3 on the VAS, $p = 0.45$) injection. In the bupivacaine group there was a substantial reduction in the score over placebo 1 h after its injection (-5.3 ± 1.4 versus -1.5 ± 1.3 , $p = 0.003$). Lidocaine was ineffective after an infusion of 4mg/kg ($p > 0.05$) during 30 minutes in 31 subjects with chronic PLP. This may be because the peripheral action of lidocaine and its minor central effect, which reduces ectopic discharge, caused lidocaine to be ineffective. Injections of local anaesthetics are known to reduce, but the precise mechanisms behind this effect are not fully understood. On the other hand, Harden et al.³³ conducted a study in which they randomly assigned 30 patients to either receive epidural bupivacaine (0.166 percent, 2-8mL/h) and diamorphine (0.2-0.8mg/h) 24 hours before, during, and 3 days after surgery (14 patients), or to receive perineural bupivacaine (0.25 percent, 10mL/h) during and after surgery (16 patients). They found that at 3 days, 6 and 12 months of follow-up, 29 percent, 63 percent and 38 percent in the epidural group had phantom ($p = 0.32$; $p = 0.25$; and $p = 0.61$, respectively). Based on these findings, they came to the conclusion that epidural blockade within 24 hours of an amputation is not more effective than local anesthesia in preventing phantom limb (PLP).

In a similar manner, Borghi et al.³⁴ carried out a prospective trial on 62 patients diagnosed with PLP. Each patient got 0.5 percent ropivacaine intra-operatively at a rate of 5 ml/h, and the treatment was maintained for an average of 30 days after the operation. If the patient's score on the Verbal Scoring

Scale (VSS) was more than one, the ropivacaine infusion was restarted, but the infusion was stopped if the patient's score remained between zero and one. At the end of the first post-operative day, 73% of patients had a score of more than 2 on the VAS; however, after a year of follow-up, the incidence of severe-to-intolerable was only 3%, and 84% of patients claimed that they were-free. They came to the conclusion that a prolonged post-operative perineural infusion of ropivacaine was beneficial in the treatment of PLP. This is likely due to the fact that it blocks the transmission of nociceptive inputs from A and C fibres for an extended length of time. Because of this, spontaneous firing is prevented, and the number of central nerve terminals that are capable of maintaining central sensitization and the permanent structural alterations in the synaptic area of the posterior horn of the spinal cord are increased.

Conclusion

PLP is an entity that is reasonably prevalent yet may be debilitating. Since it was originally documented around 500 years ago, there has been a substantial amount of progress made in our understanding of the pathogenesis and treatment of PLP. On the other hand, there is not yet a single explanation that can explain the PLP mechanism in its whole. The majority of therapies are based on guidelines for neuropathic, while specific mechanism-based treatments are still in the process of being developed. At this time, there are no randomized trials with sample numbers that assure power, or blinded for end-point assessment, to support the evidence on pharmacological or non-pharmacological therapies for PLP. This is the case even though there are studies that have been conducted. As a consequence of this, there is a need for more research that is methodologically sound in order to reach definitive findings on the efficacy of treatments and to provide more robust recommendations for clinical practice.

Conflicts of interest: The authors declare no conflicts of interest.

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