Evidence based recommendations for Physical Medicine and Rehabilitation (PM&R) interventions for the management of Phantom Limb Pain

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1. Introduction

The use of non-pharmacological and non-invasive treatment methods for phantom limb pain (PLP) after amputation is an essential element of pain therapy. Its primary position in the therapeutic setting results from patients high acceptance, low side effects and the possibility of implementing self-effective active analgesic strategies. It should also be noted that the evidence for drug therapy strategies is limited.

However, the procedures from the field of Physical Medicine and Rehabilitation (PM&R) also have limited scientific evidence base in terms of their analgesic efficacy in comparison to a suitable control treatment for a variety of reasons.

In the following, we would like to present the specialist procedures according to their main content and, in accordance with the literature currently available, make summarizing recommendations for everyday clinical practice.

The target group consists of physicians of all disciplines in outpatient practices and primary care hospitals in Ukraine. Procedures are not discussed here, if they require a complex technical effort, are in the development phase and/or are only very rarely available in special centers for the treatment of amputees.

The evaluation does not claim to be exhaustive, but addresses a user-friendly, target group-, situation- and resource-orientated treatment recommendation for the care of patients with PLP in Ukraine.

2. Methods

The treatment recommendation is based on a systematic literature analysis, which determines the respective evidence level (1-5) of the treatment options in a multi-stage process defined in advance by the project leaders. Treatment procedures that were already mentioned in guidelines and proven on the basis of systematic reviews or randomized controlled clinical trials (RCT) were indicated accordingly. A systematic literature search on these procedures was not continued. Cochrane reviews and systematic analyses were analyzed in the same way. Procedures that had not yet been assessed by guidelines or systematic analyses were finally included in the search strategy as RCTs. An analysis of research studies with a low external evidence level (< 2; Agency for Healthcare Research and Quality) was not planned in this project.

At first, a comprehensive analysis of current national and international guidelines on the treatment of PLP was carried out. After a critical evaluation of the guidelines, a recommendation of the individual proposed treatment methods was made. Procedures were documented for further review in cases of insufficient quality, inadequate actuality (results from 2015 and older) and unclear grade of recommendation. The following guidelines were identified:

- Greitemann, B., et al. Rehabilitation after major amputation of the lower extremity. AWMF Registry No. 033/044 Class: S2k.
- Schlereth, T. S2k guideline: Diagnosis and non-interventional therapy of neuropathic pain. DG Neurology 3, 21-40 (2020). https://doi.org/10.1007/s42451-019-00139-8.[1]

The second step involved analyzing high-quality systematic meta-analyses and reviews from the Cochrane Library. The following work was identified under the search term "phantom (limb) pain":

- Johnson MI, Mulvey MR, Bagnall AM. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. Cochrane Database Syst Rev. 2015 Aug 18;8(8):CD007264. doi: 10.1002/14651858.CD007264.pub3.[2]

In a third step, systematic reviews and meta-analyses were searched in the databases "pub Med" and "PEDro". Under the search term "phantom limb pain", 241 results were identified on 22/02/2024 (225 results Pub Med; 16 results PEDro). These results were then screened for thematic relevance (non-invasive and non-drug therapies in the field of PM&R) and duplicates were excluded by two experienced clinicians working in the scientific field.

In the fourth step, search terms for the literature search of RCTs in the period from 2015 to the present were defined. The search terms were determined on the basis of clinical experience in a peer group process, departmental discipline, recommendations from an Expert Consensus Delphi Study[3] published in 2021 and at last combined with the search term "phantom (limb) pain". Based on this, the specific literature search of all RCTs in PubMed and PEDro was carried out for the following procedures:

1. Mirror therapy**°
2. (Graded) motor imagery**
3. Prosthesis usage**/Use of a functional prosthesis**
4. Sensory discrimination training**°
5. Virtual reality/Augmented reality**
6. Action observation*
7. Biofeedback training*
8. Electromagnetic shielding*
9. Exercise / phantom exercise training*°
10. Intermanual transfer*
11. Laterality recognition
12. Motor imagery
13. (Progressive residual limb) Muscle relaxation (techniques)*°
14. (Residual limb) massage*°
15. Residual limb bandaging*°
16. TENS*°

(**=Consensus in Delphi; *=proposed by experts; °=Guideline recommendation)

In the final fifth step, the search results were screened and analyzed by two experienced clinicians, who work in science, in order to create a treatment recommendation based on the results. All methods were briefly described and special features highlighted.

A detailed description and instructions for the implementation of the methods cannot be given here and we refer to the international specialist literature and the expertise of our therapeutic colleagues in Ukraine.

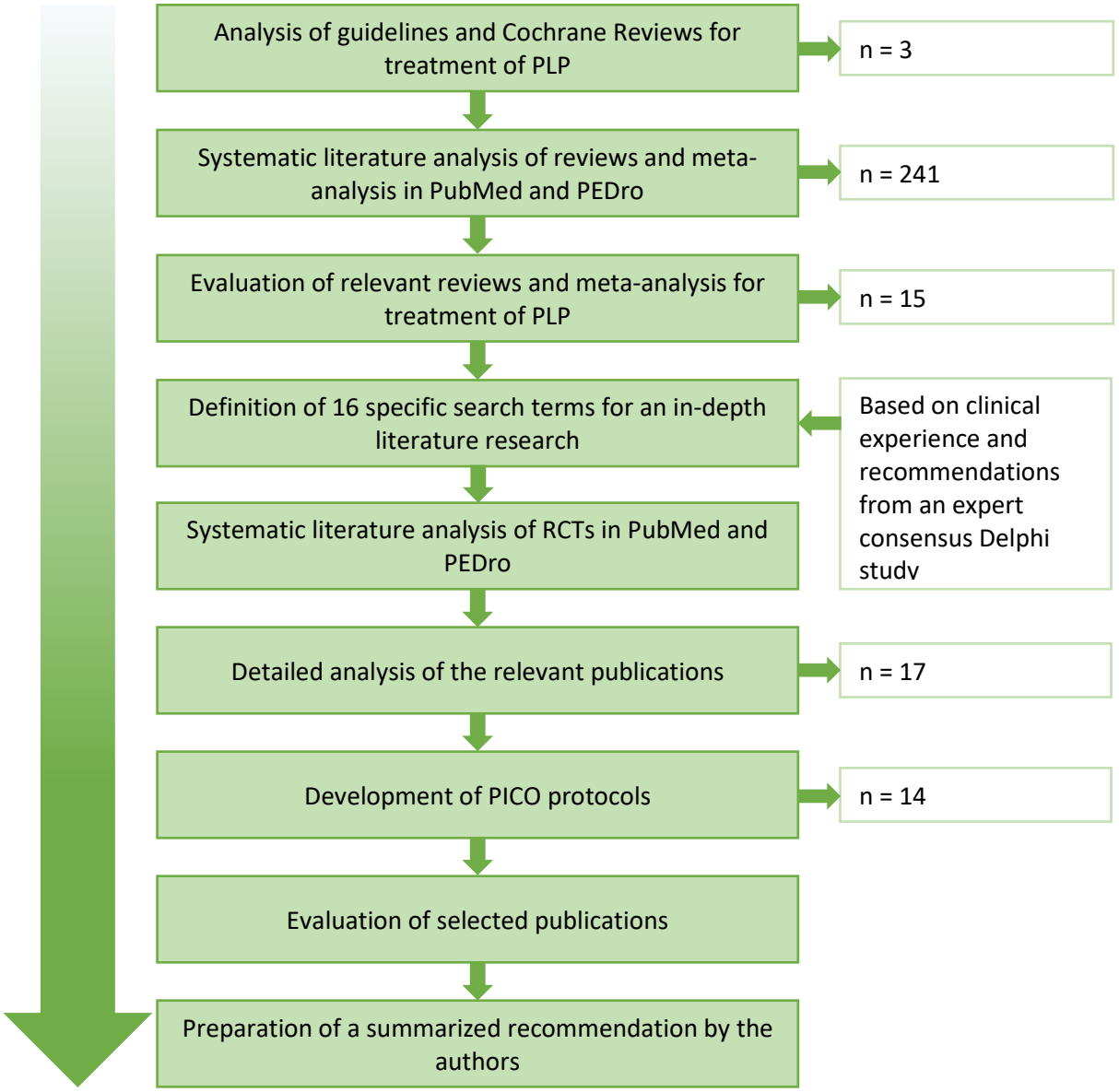


Figure 1: Flow chart of the evidence analysis

3. Results

3.1. Mirror therapy (MT)

MT, which was proposed in the early 1990s as a treatment for PLP, is easy and economical. A mirror is used to view the reflection of the uninjured side of the body. The result is an illusion of increased function or reduced pain in the missing body part. A mirror is placed in a box in front of the body so that the amputee can only see the contralateral limb as well as the reflection of this limb, and then some exercises or movements are performed. It is assumed that MT enhances the coherence between motor impulsion and sensory feedback, thus reducing the deleterious cortical reorganization and removing the pain directly. MT is also used in the treatment of other disorders, such as complex regional pain syndrome and strokes.[4]

Search results included seven publications of randomized controlled trials, systematic reviews and meta-analysis published from 2015 until 2022. All studies showed significant beneficial effects of MT in pain reduction for patients with PLP[5, 6, 7, 8] except for one systematic review[9] because the level of evidence was insufficient. A Network Meta-Analysis reports significantly lower pain intensity compared with placebo and conclude that MT is the most optimal treatment for PLP, and a combination of therapies would enhance the therapeutic effect.[5]

3.2. Graded Motor Imagery (GMI)

GMI is a therapy carried out in three ascending phases, which are divided into 1. lateralization exercises, 2. explicit motor imagery and 3. mirror therapy. It is used for cortical reorganization in the case of a hypothetical imbalance between sensory, motor and visual perceptions that can lead to PLP. In the 1st phase, left-right distinctions are made on images of the amputee (lateralization exercises). In the 2nd phase, an imaginary exercise of the missing limb is carried out using explicit motor imagery. In the third phase, mirror therapy is carried out, where a mirror is positioned so that the complete contralateral limb is mirrored to the amputee and the amputated limb cannot be seen. The amputee receives the visual information that both

limbs can be moved without pain. All phases should build on each other and allow the learning and reorganization process to progress.[10, 11]

A RCT from 2020 showed that GMI effectively reduced PLP and was significantly superior to standard treatment using individual physiotherapy.[12] A systematic review published in 2023 noted that the results suggest that GMI could be effective in reducing PLP.[13] The authors of the review justify this cautious statement with a high study bias and low study quality. In summary, a recommendation (B) for the implementation of GMI can be given based on the current data situation.

3.3. Prosthesis usage

In the current German guideline on rehabilitation after major amputation of the lower extremity, the use of a prosthesis is explicitly recommended for the treatment of chronic PLP. It is pointed out, that the amputee should be fitted with a prosthesis and mobilized as soon as possible. This based on the results of Weiss et al.[14] and Brückner et al.[15] They showed that amputees with active use of functional arm prostheses (“Sauerbruch-arm”) have significantly lower levels of phantom pain. However, the results are questionable in their significance due to methodological deficiencies. We were unable to identify any systematic analyses on this topic or RCTs. Two surveys analyzed prosthesis use outcomes like psychosocial adjustment, activity restriction, prosthesis satisfaction or prosthesis ownership. One study showed that PLP was associated with dissatisfaction with the prosthesis.[16] The frequency of prosthesis use was significantly related to the absence of PLP. Higher prosthesis ownership (defined as the extent to which a prosthesis is experienced as being part of the body rather than an artificial device foreign to the body) was associated with lower PLP.[17]

In summary, from a scientific point of view we can only give a limited recommendation due to the lack of high quality studies.

3.4. Sensory discrimination training

In sensory discrimination training, the patient is given a specific, defined and controlled stimulus. The patient is then asked to judge an aspect of the stimulus (e.g. the location) and is then given feedback on the accuracy of their judgement.[18, 19]

One systematic review[20] was identified in which two RCTs[19, 21] where taken into account. Based on the available data, no recommendation for sensory discrimination training can be made due to the low quality of the studies, the low number of participants and the high risk of bias.

3.5. Virtual Reality (VR)/Augmented Reality (AR)

The concept of VR describes a computer-generated, interactive virtual environment. This VR completely surrounds the user so that physical reality is largely hidden. The combination of VR and physical reality - for example, when digital elements are inserted into the real world using special goggles - is described as mixed reality (AR).[22] In the treatment of patients with PLP, various methods are used for visual imagination of the missing limb. Virtual motor tasks can be visualized via an interface on the remaining muscles on the residual limb, but tactile stimuli can also be transmitted using innovative prosthesis technology in order to optimize the exchange of information between the CNS and residual limb and thus contribute to a reduction in PLP. The innovative technical possibilities are being intensively evaluated and promising therapeutic approaches have been explored in mostly small case (series) studies.

Six systematic reviews were identified.[23, 24, 25, 26, 27, 28] In all studies, a PLP reduction was described on the basis of clinical pre-test post-test studies. All studies report low sample sizes, high methodological heterogeneity and limited conclusions about the evidence. Due to these methodological limitations and the lack of control interventions, these results should be considered critically. Two RCTs of higher methodological quality were identified in the primary literature,[29, 30] although they describe controversial results. No significant superiority to the control intervention (Sham-VR; SDT) could be shown here.

3.6. Action Observation

Observation in combination with visualization of movements is intended to influence maladaptive plasticity after amputation and to reduce PLP. Patients are trained to mentally evoke and control the images and sensations of movements that they perform with their missing limb. The approach appears practicable, as simple options (videos/images) can be used to practice independently after initial instruction, largely irrespective of the physical condition (e.g. post-operative immobility).

However, RCTs and systematic analyses are lacking. In a case series reported in 2011, action observation was combined with imagination in six amputees suffering from PLP. Four of the six study participants were able to reduce their PLP by >30%.[31] Due to the insufficient study situation, we cannot give a recommendation for action observation.

3.7. Biofeedback Training

Biofeedback training is used for sensory feedback by performing phantom movements and usually involves visual or tactile information. This information can be transmitted via different interfaces such as a screen or directly via the contact surface of the prosthesis. The aim is to equalize the sensorimotor incongruence between motor intention and proprioceptive feedback and to approximate the original physiological processes despite the missing limb part. This balancing of information is intended to counteract maladaptive plasticity by inducing somatosensory plasticity, reduce PLP and optimize compensatory movement patterns of the muscles.

Search results included six publications of a single-blind randomized crossover feasibility trial, case series, within subject designs and case studies with low sample sizes published from 2012 until 2022. All studies showed significant beneficial effects of biofeedback devices in terms of pain reduction using visual analogue scale for patients with PLP.[32, 33, 34, 35, 36, 37] Due to the low level of evidence, results only provide indications of an effect of biofeedback training on PLP, but this still needs to be confirmed in RCTs.

3.8. Electromagnetic shielding

The use of electromagnetic shielding liners is being discussed and the scientific background as well as the mechanism of action is still unclear. Nevertheless, amputees report an increased likelihood of PLP occurring when the weather changes and, in particular, when storms occur that are associated with a change in electromagnetic environmental fields.

We were unable to find any guidelines, reviews or systematic meta-analyses of this form of therapy. In two RCTs, the intervention was performed in comparison to the control with liners without electromagnetic shielding.[38, 39] One of the two studies showed positive differences in PLP compared to the control group. However, a recommendation cannot be given at this time due to the small number of participants and the methodological deficits.

3.9. (Phantom) exercise training / Imagined limb-movement exercises

In phantom exercises, the imaginary movement of the phantom limbs is combined in the central nervous system with the execution of certain actual physical movements. The neurophysiological network, involved here, is similar to that of actual physical activities of healthy limbs.

We were unable to find any guidelines, reviews or systematic meta-analyses of this form of therapy. In Ulger's 2009 study, phantom exercises were tested in comparison to training therapy. Both groups also received prosthesis training. After 4 weeks, a reduction in pain was shown in both groups. Participants in the phantom exercise group showed significantly greater pain reduction after 4 weeks than the control group.[40] In an RCT from 2021, phantom exercise training was added to standard of care, including mirror therapy and physiotherapy, and it was compared with standard of care. After 4 weeks of therapy, a significant reduction in pain over time was shown in both groups. Additional significant differences were found between the groups after 4 weeks in favor of the phantom exercise-training group with greater pain reduction. Based on this RCT with 24 participants, both therapy approaches can be effectively recommended for the pain relief of PLP. An additional benefit from the use of phantom exercises was shown after 4 weeks.[41] Phantom exercises can be recommended with restrictions, but robust data with larger case numbers specifically for chronic PLP are lacking.

3.10. Intermanual transfer

Through the intermanual transfer between the missing and existing limb - or parts of the limb -, motor functions learnt with one limb are transferred to the other limb. The learning of motor functions is in turn closely linked to the perception of PLP. In this way, it was postulated that reactivation of the cortical motor representation can influence the PLP.[42] To date, we were unable to find any study that has investigated the dedicated influence of intermanual transfer on PLP in comparison to a control group. As a result, we cannot make a recommendation from a scientific perspective.

3.11. Lateralization exercises / Lateralyti recognition

Laterality exercises are movement visualization techniques and part of GMI. Here, patients are shown numerous images of right and left limbs from different positions. Patients have to perform laterality recognition as fast as possible. The exercises should be performed frequently/daily over a period of >4 weeks. An increase in PLP has also been described in patients with poor visualization or incorrect implementation of the therapy. The authors therefore recommend testing the visual and kinesthetic capacity (Kinesthetic and Visual Imagery Questionnaire, KVIQ) of patients in advance to avoid adverse effects.[43] In the context of GMI, some authors see laterality recognition as a preparatory technique for the implementation of mirror therapy.[44]

This therapy has been shown to be analgesically effective in patients with CRPS, but we could only find one RCT on the effect on PLP. In this study from 2021, impairment of body representation was the primary outcome. A secondary analysis of the data also showed that approximately 80% of study participants reported reduced pain intensity when performing lateralization exercises, and the authors therefore recommend testing the efficacy of image-based treatment procedures with PLP as the primary outcome.[45] Due to the lack of studies, we are unable to make a firm recommendation for lateralization exercises.

3.12. Motor Imagery

A clinical study showed that regular mental imagery exercises of the amputated limb, learned through therapeutic guidance in a calm environment, led to pain relief associated with a reduction in cortical reorganization.[46] These techniques are simple, safe and can be practiced by the patient.

In 2016, Thieme et al. examined the effectiveness of movement visualization techniques for the treatment of limb pain in a systematic review and found no pain-reducing effect in PLP.[47] Based on the current data situation, no recommendation can be made at this time from a scientific perspective regarding the implementation of motor imagery techniques.

3.13. (Progressive residual limb) muscle relaxation (techniques)

There is a variety of relaxation techniques, all of that aim to optimize body awareness and consciously achieve muscular relaxation and counteract physical, mental and vegetative restlessness. These methods are generally associated to psychotherapy and serve to increase self-efficacy and general well-being. Positive effects have been shown for anxiety and mental agitation, chronic pain, stress, sleep disorders, arterial hypertension and headaches.

No systematic analyses and reviews could be identified for the treatment of PLP. In the only randomized clinical trial on the treatment of PLP with relaxation techniques that is currently available to us, a superiority compared to the control intervention was demonstrated.[48] However, these results are only of limited significance, as the intervention was combined with other effective therapy methods (MT, MI) and compared with exercise. The extent to which the relaxation techniques alone generate positive effects on PLP remains unclear. To summarize, no recommendation for relaxation techniques can be made from a scientific perspective due to the lack of research results. Due to the low number of contraindications and adverse events, it makes sense from a clinical perspective to integrate them into a multimodal therapeutic setting on a trial basis. In addition, stress, sleep, pain perception and restlessness can be usefully treated with relaxation techniques.

3.14. (Residual limb) Massage

In the current German guideline on rehabilitation after major amputation of the lower extremity, "brush massages" and "reflexology massages" are explicitly recommended for the treatment of chronic PLP under the heading "physical measures". However, there are no references to the literature here.**Fehler! Textmarke nicht definiert.**

In the subsequent search, neither a systematic analysis nor a RCT on this topic could be found. One pilot study evaluated the use of reflexology and showed positive effects, but there was no control group and the specific effects cannot be assessed.[49] Based on current data, no recommendations can be made for the use of massage techniques in the treatment of PLP. However, valuable non-specific effects in chronic pain patients on depression, stress, anxiety, fatigue, pain thresholds[50] and sleep as well as myofascial dysfunction[51] should definitely be used if indicated to reduce/compensate for pain medication and to bridge the effects (e.g. overdosing of antidepressants).

3.15. Residual limb bandaging

The current German guideline on rehabilitation after major amputation of the lower limb explicitly recommends "compression, e.g. with a liner or residual limb stocking outside the wearing period of the prosthesis" for the treatment of chronic PLP under the heading "physical measures".**Fehler! Textmarke nicht definiert.** The implementation of swelling-reduction treatments is of significant importance in the postoperative phase in order to support both wound healing and volume constancy for prosthetic treatment. In addition to bandaging, manual lymphatic drainage and muscular activation are used as part of complex decongestive therapy.

However, there are no references to the literature here. In the following analysis of the literature, neither a systematic analysis nor a RCT on efficacy in PLP could be found that could scientifically substantiate its use.

3.16. Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is a technique in which pulsed electrical currents are delivered through the intact skin surface to stimulate peripheral nerves. TENS is

mainly used to relieve pain and is usually applied using a portable, battery-operated device. This TENS device generates electrical currents that are conducted through the skin via electrodes attached to the surface of the skin. The analgesic effects are based on stimulation of A-beta afferents (segmental analgesia) and A-delta afferents (extrasegmental analgesia). This leads to an inhibition of nociceptive neurons, increases blood flow and reduces muscle spasms. As a result, it is plausible that TENS could alleviate PLP, residual limb pain or both. TENS is contraindicated in patients with electronic implants. Relative contraindications include pregnancy, epilepsy, active malignancy, deep vein thrombosis and damaged skin.[2]

In the current German guideline on rehabilitation after major amputation of the lower extremity,[Fehler! Textmarke nicht definiert.] the effect of TENS for the treatment of chronic PLP is assessed as contradictory. This conclusion is based on a meta-analysis on the treatment of postoperative pain from 2003.[52] The systematic review of the Cochrane Database by Johnson et al (2015) found insufficient evidence from RCTs to assess whether or not TENS should be used in the treatment of PLP and residual limb pain in adults.[2] TENS is safe, cost-effective and can be self-administered by guided patients. Therefore, from a clinical point of view, we recommend trial use to test analgesic effects on an individual basis.

4. Conclusion

Based on the detailed analysis of the literature, recommendation can be made from a scientific perspective for therapeutic methods from the field of PM&R for the treatment of PLP. Table 1 summarizes the evidence for the individual therapeutic methods. (s. Table 2).

Mirror therapy is recommended as a proven analgesically effective form of therapy. The therapeutic effect can be increased by combining it with other treatments. **Virtual/Augmented realty** procedures can be used for complex injury patients with multiple amputations. As part of **graded motor imagery**, mirror therapy can also be applied using lateralization exercises and motor imagery procedures in a graded learning and reorganization process. This may be indicated, for example, if the amputee has insufficient visualization skills or if re-traumatizing flashbacks occur in the case of PTSD. No sufficient scientific evidence for a recommendation could be found for **Laterality recognition exercises** and **motor imagery** as monotherapies. A recommendation for **Virtual/Augmented Realty** is also only possible to a limited extent due to a lack of methodologically high-quality comparative studies.

Phantom exercise can be recommended based on two RCTs that showed significant analgesic effects compared to the control group. For **sensory discrimination training**, a systematic review criticized the low quality of the two primary RCTs, meaning that no recommendation can be made. Intensive **use of a (functional) prosthesis** may contribute to a reduction in PLP, but the scientific evidence for this is not clear, so a limited recommendation can be made. The same applies to **biofeedback training**, where the results of clinical studies show PLP-reducing effects. Again, there is a lack of RCTs to make a clear recommendation.

Electromagnetic shielding of the residual limb was tested in two RCTs, one study showed positive effects compared to the control group. Due to the small number of cases and the methodological shortcomings, no recommendation can be made. **Relaxation techniques** were tested as an add-on in a multimodal therapy approach and classified as analgesically effective. However, due to the methodological limitations, no recommendation can be made from a scientific perspective based on the current literature.

Unfortunately, there are no RCTs for **action observation, massage techniques, residual limb bandaging, intermanual transfer** and **TENS** to make a recommendation.

Irrespective of the evidence, however, procedures with a low spectrum of side effects and a potential increase in patient strategies and self-efficacy are recommended based on subjective clinical expertise (evidence level 5). First and foremost, **physiotherapy** should be mentioned here, which makes a significant contribution in improving the general condition and optimizing function on numerous levels, especially in the acute phase. Physiotherapeutically supervised exercise, if possible with the use of the prosthesis, should also be carried out for many reasons. In addition to raising the pain threshold, improving mood and general well-being, the use of the prosthesis can be intensified in small exercise groups and embodiment can be initiated. Handling the prosthesis in everyday life (ADLs) as part of traditional **occupational therapy** can also significantly support this process. In addition to **TENS, relaxation techniques** and **massage techniques** are also recommended as useful components in the multimodal therapy concept for the treatment of chronic pain and depression in order to reduce the use of analgesics and co-analgesics.

Method	Evidence level			
	1	2	3	>3
Mirror therapy	•			
(Graded) motor imagery		•		
Exercise / phantom exercise training		•		
Prosthesis usage / Use of a functional prosthesis			•	
Sensory discrimination training			•	
Virtual reality/Augmented reality			•	
Biofeedback training			•	
Motor imagery				•
Electromagnetic shielding				•
Laterality recognition				•
Action observation				•
(Progressive residual limb) Muscle relaxation (techniques)				•
(Residual limb) massage				•
Residual limb bandaging				•
TENS				•

Table 1: Evidence level of different therapeutic methods.

Method	Recommendation		
	A	B	O
Mirror therapy	•		
(Graded) motor imagery		•	
Exercise / phantom exercise training		•	
Prosthesis usage / Use of a functional prosthesis		•	
Sensory discrimination training		•	
Virtual reality/Augmented reality		•	
Biofeedback training		•	
Motor imagery			•
Electromagnetic shielding			•
Laterality recognition			•
Action observation			•
(Progressive residual limb) Muscle relaxation (techniques)			•
(Residual limb) massage			•
Residual limb bandaging			•
TENS			•

Table 2: Evidence-based therapy Recommendation of the authors

In summary, there is a great need for methodologically high-quality clinical RCTs that evaluate methods for the treatment of PLP. There are numerous reasons why methodological and ethical/moral barriers make it difficult to conduct this type of study. A lack of comparable control interventions, sufficiently comparable study participants and high heterogeneity of the population to be analyzed as well as the great methodological diversity of innovative approaches ultimately lead to a lack of high-quality RCTs. Resulting systematic analyses are hardly possible due to these facts. It should be noted that, in particular, basal forms of therapy that, in addition to the targeted treatment of PLP, also include general mobility, the avoidance of immobilization-related deconditioning and its extensive consequences, such as physiotherapy, cannot be denied to a control group for ethical reasons. Innovative methodological ideas and evaluation methods with which this range of therapies can be tested are crucial here.

5. PICO protocols

5.1.1. Mirror therapy

PICO question	Does mirror therapy lead to a detectable pain reduction in patients with phantom pain of any cause compared to usual care or placebo?	
List of sources	**Evidence level**	**Study type**
1 Comparative Effects of Interventions on Phantom Limb Pain: A Network Meta-Analysis.	1	Network Meta-Analysis
2 Effectiveness of Mirror Therapy for Phantom Limb Pain: A Systematic Review and Meta-analysis.	1	A Systematic Review and Meta-analysis
3 Effects of phantom exercises on pain, mobility, and quality of life among lower limb amputees; a randomized controlled trial.	2	Randomized controlled trial
4 Effectiveness of mirror therapy, motor imagery, and virtual feedback on phantom limb pain following amputation: A systematic review.	1	Systematic review
5 Mirror Therapy and Transcutaneous Electrical Nerve Stimulation for Management of Phantom Limb Pain in Amputees - A Single Blinded Randomized Controlled Trial.	2	Randomized controlled trial
6 The effects of mirror therapy on pain and motor control of phantom limb in amputees: A systematic review.	1	Systematic Review
7 Effects of mirror therapy on phantom limb sensation and phantom limb pain in amputees: A systematic review and meta-analysis of randomized controlled trials.	1	A systematic review and meta-analysis of randomized controlled trials.

Source	**P-I-C**	**Outcome**	**Results**
1 Wang J, Fan J, Gc R, Zhao J. Comparative Effects of Interventions on Phantom Limb Pain: A Network Meta-Analysis. World Neurosurg. 2023 Feb;170:e45-e56. doi: 10.1016/j.wneu.2022.10.060. Epub 2022 Oct 21. PMID: 36273725.	Population: Patients with PLP who received treatment for pain control rather than prevention Intervention: All types of interventions given solely or in combination, in any dose, by any route were eligible, including mirror therapy, motor cortex stimulation, phantom exercise, local anaesthesia,	Primary: pain intensity measured by either the visual analog scale or numeric rating scale. Secondary:	RESULTS: Twenty-two studies comprising 662 patients and 13 different interventions were included in this study. The mirror therapy (MT) (-1.00; 95% confidence interval, -1.94 to -0.07) and MT + phantom exercise (PE) (-6.05; 95% confidence interval, -8.29 to -3.81) group presented significantly lower pain intensity compared with placebo. In SUCRA (surface under the cumulative ranking curve) analysis, the MT+PE and neuromodulation techniques groups had the highest SUCRA value (81.2).

	pharmacotherapy, and so on.		CONCLUSIONS: Our results suggest that MT is the most optimal treatment for PLP, and a combination of therapies would enhance the therapeutic effect.
	Comparison: usual inpatient care, mirror therapy with a covered mirror, sham stimulation, and injections with saline.		
	Methodological notes Funding source (public/industry/internal): COI declared (yes/no): No conflict is declared Study Quality: Assessment of risk of bias: low - unclear risk of bias Publication bias: not assessable Number of references: 58 Limits: Only 22 studies included with relatively small sample sizes lacking of long-term data as well as heterogeneity in terms of trial design, medication, dosage and time of follow-up.		

Source	**P-I-C**	**Outcome**	**Results**
2 Xie HM, Zhang KX, Wang S, Wang N, Wang N, Li X, Huang LP. Effectiveness of Mirror Therapy for Phantom Limb Pain: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil. 2022 May; 103(5):988-997. doi: 10.1016/j.apmr.2021.07.810. Epub 2021 Aug 28. PMID: 34461084.	Population: RCTs that assessed the effect of Mirror therapy (MT) for Phantom Limb Pain (PLP) were included. The patients enrolled had PLP after amputation.	Primary: Pain intensity of MT for PLP by visual analog scale	RESULTS: Meta-analysis revealed a statistically significant decrease in pain in the MT group vs the control group within 1 month (I^2=0%; standardized mean difference [SMD] =-0.46, 95% confidence interval [CI], -0.79 to -0.13; P = .007). The patients with pain for longer than 1 year benefited more from MT (I^2=0%; SMD=-0.46; 95% CI, -0.85 to -0.07; P = .02). CONCLUSIONS: MT has beneficial effects for patients with PLP in the short-term, as evidenced by their improved pain scores. There was no evidence that MT had a long-term effect, but that may be a product of limited data. For patients with long-term PLP, MT may be an effective treatment. In summary, MT showed significant beneficial effects on pain reduction for patients with PLP in the short-term, even if the longterm efficacy is uncertain. Therefore, additional high-quality RCTs may be required to support the conclusions of the present meta-analysis. For patients experiencing longstanding PLP, MT may be an effective treatment. Additionally, there may be a trend toward better efficacy with combination therapy. Further research should focus on the duration and frequency of therapy as well as mental factors in patients. Further research is needed on long-term efficacy of this therapy not only from the
	Intervention: The patients enrolled had PLP after amputation. The MT group (MT group) used MT as an intervention.	Secondary: The PEDro scale was used to assess the methodological quality of studies.	
	Comparison: The control group used non-MT (covered mirror, tactile treatment, phantom exercise, mental visualization therapy, or physiotherapy).		

			aspect of pain reduction but also of quality of life.
	Methodological notes Funding source (public/industry/internal): Supported by the grants of Foundation and Strengthening Program in Technical Area of China (grant no. 2019-JCJQ-JJ-149) and the Capital Health Research and Development of Special (2020-2Z-5015). Registration No.: CRD42021232914. COI declared (yes/no): not found Study Quality: The methodological quality of all the 10 articles could be regarded as moderate. Eight of the 10 studies were rated between 4 and 7 of 10 on the PEDro scale. Eight was the highest score because data on the blinding of participants and blinding of the therapists were not available. The only study with a score of 8 was that of Rothgangel et al.18 Other than blinding, the 2 categories with the most points lost were allocation concealing and evaluator blinding. Publication bias: not assessable Number of references: 38 Notes:		
Source	**P-I-C**	**Outcome**	**Results**
3 Zaheer A, Malik AN, Masood T, Fatima S. Effects of phantom exercises on pain, mobility, and quality of life among lower limb amputees; a randomized controlled trial. BMC Neurol. 2021 Oct 27;21(1):416. doi: 10.1186/s12883-021-02441-z. PMID: 34706654; PMCID: PMC8554869.	Population: Unilateral lower limb amputees (above and below the knee)	Primary: VAS (pain)	Results: After the intervention, the pain (VAS score) was significantly lower in the experimental group ($p = 0.003$). Similarly, the experimental group demonstrated a significantly better score in the " bodily pain" domain of SF-36 ($p = 0.012$). Both groups significantly ($p < 0.05$) improved in other domains of SF-36 and ambulatory potential with no significant ($p > 0.05$) between-group differences. Conclusions: The Addition of phantom exercises resulted in significantly better pain management in lower limb amputees treated with mirror therapy and routine physiotherapy.
	Intervention: Experimental group is given phantom exercises, additionally to mirror therapy and conventional physical therapy	Secondary: AMP (mobility) and RAND SF-36 Version 1.0 (QOL)	
	Comparison: control group (mirror therapy and conventional physical therapy)	Additionally exercises are described in detail (see pages 3-4).	
	Methodological notes Funding source (public/industry/internal): No funding sources COI declared (yes/no): Yes, no conflict Study Quality: Publication bias: not assessable Number of references: 34 Notes: This article was a research thesis project written for the Master of Science in Neuromuscular Physical therapy (MSNMPT) programme. Limits: The main limitation of our study is that rehabilitation centres were closed because of the pandemic situation, which caused to difficulty in data collection and small sample size, which lead to the difficulty in generalizing the study findings. Another limitation is that location and cause of lower limb amputation were not taken into account while calculating results. Similarly, the absence of a record for the medication history might have influenced the findings. Myoelectric study of the residual limb may also increase the objectivity of the results.		
Source	**P-I-C**	**Outcome**	**Results**
4 Herrador Colmenero L, Perez Marmol JM, Martí-García C, Querol Zaldivar MLÁ, Tapia Haro RM, Castro Sánchez AM, Aguilar-Ferrándiz ME. Effectiveness of	Population: studies focused on amputees or stumps with PLP	Primary:	RESULTS: The largest sample of amputees in the experimental group was 41 patients, and the lowest, 5 patients. Four papers presented a
	Intervention:	Secondary:	

mirror therapy, motor imagery, and virtual feedback on phantom limb pain following amputation: A systematic review. Prosthet Orthot Int. 2018 Jun;42(3):288-298. doi: 10.1177/0309364617740230. Epub 2017 Nov 20. PMID: 29153043. CAVE: Its including several therapies not only mirror therapy	Included were studies using mirror therapy, motor imaginary or virtual visual feedback; including study designs like experimental studies, randomized controlled trials (RCTs); using the adult population.	The PEDro scale was used to evaluate the methodological quality of the included studies, selecting only articles scoring over 3 points	sample of upper limb amputees, three studies used lower limb amputees, and six used a mixed sample of upper and lower limb. According to the classification of the Cochrane Back Review Group, there was limited evidence for mirror/virtual therapy and motor imagery because there were no high-quality RCTs. This review evaluated the effectiveness of mirror therapy, motor imagery, and virtual visual feedback in amputees with PLP. All studies examined showed an effective improvement in perceived pain; however, according to the criteria specified by the Back Review Group, there was limited evidence for the use of these therapies in reducing PLP. This lack of evidence can be explained because previous research used pilot studies or case study designs where the treatment protocols were not adapted to clinical practice. Moreover, the overall number of studies on this topic is low. Heterogeneity has been observed in the type and intensity of PLP within and among studies, especially before treatment. However, all studies showed a significant reduction of PLP. In conclusion, all the studies reported a significant decrease in pain, regardless of the technique used. However, the evidence for the effectiveness of these techniques for PLP reduction in amputees was classified as limited.
	Comparison:		
	Methodological notes Funding source (public/industry/internal): No funding COI declared (yes/no): No conflict is declared. Study Quality: na Publication bias: na Number of references: 47		
Source	**P-I-C**	**Outcome**	**Results**
5 Tilak M, Isaac SA, Fletcher J, Vasanthan LT, Subbaiah RS, Babu A, Bhide R, Tharion G. Mirror Therapy and Transcutaneous Electrical Nerve Stimulation for Management of Phantom Limb Pain in Amputees - A Single Blinded Randomized Controlled Trial. Physiother Res Int. 2016 Jun;21(2):109-15. doi: 10.1002/pri.1626. Epub 2015 Apr 1. PMID: 25832306	Population: Unilateral amputees between the age of 18 and 60. Subjects with visual and sensory impairment, bleeding disorders and those with bilateral amputation were excluded from the study.	Primary: The primary outcome measure was pain intensity, which was measured using Visual analogue scale and Universal pain score.	Participants of Group I had significant decrease in pain [VAS (p = 0.003) and UPS (p = 0.001)]. Group II also showed a significant reduction in pain [VAS (p = 0.003) and UPS (p = 0.002)]. However, no difference was observed between the two groups [VAS (p = 0.223 and UPS (p = 0.956)]. Discussion: Both Mirror Therapy and TENS were found to be effective in pain reduction on a short-term basis.
	Intervention:	Secondary:	

	Mirror training is thought to reverse the cortical reorganizational changes related to PLP	Not applicable	However, no difference between the two groups was found. Substantiation with long-term follow-up is essential to find its long-term effectiveness.
	Comparison: The contralateral limb application of TENS sends afferent impulses, which passes through the transcallosal fibres and activates cortical areas, which represent the deafferented limb.	This study was a single blinded randomized controlled trial in which the outcome assessor was blinded to the treatment received by the subjects.	
	Methodological notes Funding source (public/industry/internal): Monetary support was taken from the institutional research grant, which is an internal fund from Christian Medical College, Vellore. COI declared (yes/no): No Study Quality: NA Publication bias: NA Number of references: 17 Limits: All possible measures were taken to ensure the study had low level of bias including randomization, allocation concealment, blinding of the outcome assessor, similar baseline characteristics and sample size calculation. However, the present study had a few limitations. Firstly, the blinding of the therapist or the study subjects was impossible because of the nature of the intervention given. Secondly, the homogeneity in the two groups using stratified randomization was not followed with respect to the level of amputation, because of lack of vast samples. Thirdly, the treatment period was very short (4 days) for subjects in both groups, because of practical difficulty of subjects coming for treatment to the hospital. Other limitations include duration and frequency of PLP among the subjects, lack of placebo or non-treatment group and lack of long-term follow-up. These factors may have limited the response of these interventions.		
Source	**P-I-C**	**Outcome**	**Results**
6 Barbin J, Seetha V, Casillas JM, Paysant J, Pérennou D. The effects of mirror therapy on pain and motor control of phantom limb in amputees: A systematic review. Ann Phys Rehabil Med. 2016 Sep; 59(4):270-5. doi: 10.1016/j.rehab.2016.04.001. Epub 2016 May 30. PMID: 27256539.	Population: Amputees	Primary: pain and motor control	Results: Twenty studies were selected, 12 on the subject of MT and PLP, 3 on MT and PLM, 5 on MT and both (PLP and PLM). Among these 20 studies, 5 were randomized controlled trials (163 patients), 6 prospective studies (55 patients), 9 case studies (40 patients) and methodologies were heterogeneous. Seventeen of the 18 studies reported the efficacy of MT on PLP, but with low levels of evidence. One randomized controlled trial did not show any significant effect of MT. As to the effect of MT on PLM, the 8 studies concerned reported effectiveness of MT: 4 with a low level of evidence and 4 with a high level of evidence. An alternative to visual illusion seems to be tactile or auditory stimulation.
	Intervention: Mirror therapy	Secondary:	
	Comparison: Phantom Limb Movement	Side effects of MT: Not systematically reported. Aggravation of the PLS and/or PLP, phenomenon of telescopic distortion. The perception of the reflected image of the lost limb can also aggravate a	

		depressive syndrome. When deleterious side effects are systematically sought, they are sometimes frequent, in particular with episodes of confusion and dizziness.	Conclusion: We cannot recommend MT as a first intention treatment in PLP. The level of evidence is insufficient. Further research is needed to assess the effect of MT on pain, prosthesis use, and body representation, and to standardize protocols.
	Methodological notes Funding source (public/industry/internal): COI declared (yes/no): Yes, no conflict Study Quality: NA Publication bias: NA Number of references: 51		
Source	**P-I-C**	**Outcome**	**Results**
7 Wang F, Zhang R, Zhang J, et al. Effects of mirror therapy on phantom limb sensation and phantom limb pain in amputees: A systematic review and meta-analysis of randomized controlled trials. Clinical Rehabilitation. 2021; 35(12):1710-1721. doi:10.1177/02692155211027332	Population: When searched databases allowed limits, searches were restricted to human beings, clinical trials, English, and Chinese. The following keywords were used to obtain potential articles: amputation, loss limb, pain, phantom limb, mirror therapy, visual feedback.	Primary: Mirror therapy	Results: A total of 11 RCTs involving 491 participants were included in this review and nine RCTs involving 372 participants were included in meta-analysis. The quality of these studies was from poor to good with scores ranging from 2 to 8 points according to PEDro scale. The pooled SMD showed that mirror therapy reduced the pain with a large effect size (−0.81; 95% CI = −1.36 to −0.25; P = 0.005; I2 = 82%; n = 372) compared with other methods (four covered mirror, one phantom exercise, three mental visualizations, one sensorimotor exercise, one transcutaneous electrical nerve stimulation, one tactile stimuli). The quality of evidence for the outcome pain intensity was determined to be fair according to GRADE approach. Conclusion: There is fair-quality evidence that MT is beneficial for reducing phantom limb pain.
	Intervention: Mirror therapy	Secondary:	
	Comparison:		
	Methodological notes Funding source (public/industry/internal): This work was supported by the Project of the Science and Technology Department in Sichuan province (Grant No. 2019YJ0119). COI declared (yes/no): Yes, no conflict Study Quality: NA Publication bias: NA Number of references: 31 Limits: There are several limitations in our systematic review. First, the number of included RCTs was small (n = 11) and relatively small sample sizes in each study (ranging from 6 to 46 in mirror therapy groups). Second, studies were implemented with high heterogeneity: they differed from the duration and frequency of the mirror therapy sessions delivered to the experimental group, from the types of intervention delivered to the control group, for example, covered mirror; mental visualization; transcutaneous electrical nerve stimulation; tactile stimuli and sensorimotor exercises, and the time point to assess. Third, the		

	effects at long-term follow-up have to be considered with caution since they were based only on three studies. In future studies, the procedure for mirror therapy should be standardized, and larger sample sizes are needed to determine the efficacy of mirror therapy accurately. In conclusion, the present study provides the latest evidence to support the implementation of mirror therapy as an alternative treatment to reduce phantom limb pain in amputees compared with the control in the short term. It is recommended that further research including larger sample sizes and longer follow-up period studies in consideration of various covariates, such as frequency and duration of pain, amputation level, and mirror therapy application, should be performed.

5.1.2. (Graded) motor imagery

PICO question	Does GMI lead to a detectable pain reduction in patients with phantom pain of any cause compared to routine care or placebo?		
List of sources	**Evidence level**	**Study type**	
1 The Efficacy of Graded Motor Imagery and Its Components on Phantom Limb Pain and Disability: A Systematic Review and Meta-Analysis.	2	Systematic Review and Meta-Analysis	
Source	**P-I-C**	**Outcome**	**Results**
1 Limakatso K, Cashin AG, Williams S, Devonshire J, Parker R, McAuley JH. The Efficacy of Graded Motor Imagery and Its Components on Phantom Limb Pain and Disability: A Systematic Review and Meta-Analysis. Can J Pain. 2023 May 17; 7(1):2188899. doi: 10.1080/24740527.2023.2188899. PMID: 37214633; PMCID: PMC10193907.	Population: 373 adult Participants with PLP	Primary: Change in PLP severity assessed by a VAS (0-100mm) or NRS (0-10)	This systematic review found weak but promising evidence that GMI is more effective than routine care for producing a clinically meaningful change in pain severity.
	Intervention: Graded Motor Imagery	Secondary: Disability, HRQoL, adverse effects, psychosocial function, and patient global impression of change	
	Comparison: Routine Care		
	Methodological notes Funding source (public/industry/internal): None COI declared: The authors have no conflicts of interest. Study Quality: OK Publication bias: high risk of bias Number of references: 58 Limits: The included studies represented few upper limb amputees.		

5.1.3. Prosthesis usage

PICO question	Does Prosthesis Use lead to a detectable pain reduction in patients with phantom pain of any cause compared standard care or other therapies?

List of sources	Evidence level	Study type
1 Weiss T, Miltner WH, Adler T, Brückner L, Taub E. Decrease in phantom limb pain associated with prosthesis-induced increased use of an amputation stump in humans. Neurosci Lett. 1999 Sep 10; 272(2):131-4. doi: 10.1016/s0304-3940(99)00595-9. PMID: 10507559.	3	Non-randomized trial
2 Desmond, D., Gallagher, P., Henderson-Slater, D., & Chatfield, R. (2008). Pain and psychosocial adjustment to lower limb amputation amongst prosthesis users. Prosthetics and orthotics international, 32(2), 244–252. https://doi.org/10.1080/03093640802067046	5	Survey / Cross sectional study
3 Bekrater-Bodmann, R., Reinhard, I., Diers, M., Fuchs, X., & Flor, H. (2021). Relationship of prosthesis ownership and phantom limb pain: results of a survey in 2383 limb amputees. Pain, 162(2), 630–640. https://doi.org/10.1097/j.pain.0000000000002063	5	Survey

Source	P-I-C	Outcome	Results
1	Population: Recruited patients from researchers own practice (Sauerbruch group) and Newspaper	Primary: Pain (VAS)	The main finding of this study is that wearing a Sauerbruch prosthesis is followed by a dramatic reduction in the amount of PLP experienced by the amputees in the present sample of subjects. In addition there was no difference between groups in the number of patients reporting telescoping (shortening) of the phantom limb at the time of the study.
	Intervention: Upper Limb Sauerbruch prosthesis	Secondary: non-painful phantom limb sensation (PLS), stump pain and telescoping	
	Comparison: Upper Limb cosmetic prosthesis		
	Methodological notes Funding source: BMFT grant 01 ZZ 9602 and DFG grant Mi 265±1 (to W.H.R.M.) and grant B95± 975R from the Rehabilitation Research Service of the Veterans Administration (to E.T.). COI declared: No Study Quality: Publication date is 1999, due to this reporting standards like in terms of structure or consort statement are not used. Publication bias: na Number of references: 19 Notes: Upper limb prosthesis Limits: Median range of age differs signifanctly in group “Sauerbruch” 34 Years from group “Cosmetic” of median age of 63 years. Methodical quality is lacking!		

Reference	P-I-C	Outcome	Results
2	Population: Eighty-nine people with a lower limb amputation	Primary: associations between post-amputation phantom and residual limb pain and prosthesis satisfaction, activity restriction and psychosocial adjustment to amputation among lower limb prosthesis users	Characteristics of phantom and residual limb pain, prosthesis satisfaction, activity restriction and psychosocial adjustment to amputation were assessed using the Trinity Amputation and Prosthesis Experience Scales (TAPES). Comparisons of those who **experienced residual and/or phantom limb pain** in the preceding assessment with those who did not revealed **significant differences in prosthesis satisfaction, psychosocial adjustment** but not in activity restriction. Overall, it is important for clinicians to ascertain the type and level of pain that the person is experiencing and to separate the experiences of the pain from the experiences of the prosthetic limb. The experience of residual limb pain and/or phantom limb pain in the last week is associated with the dissatisfaction with the prosthesis.
	Intervention: Postal survey	Secondary:	
	Comparison: Non		
	Methodological notes Funding source (public/industry/internal): COI declared (yes/no): Yes, no conflict Study Quality: Publication bias: Number of references: 22 Notes: Not relevant for our study		
Reference	**P-I-C**	**Outcome**	**Results**
3	Population: 2383 unilateral prosthesis-using upper-limb or lower limb amputees	Primary: **Phantom Limb Pain** interacting with **Prosthesis ownership** (defined as the extent to which a prosthesis is experienced as being part of the body rather than an artificial device foreign to the body)	Frequency of prosthesis use was significantly related to the absence of PLP. Higher prosthesis ownership was associated with lower PLP. Lower limb amputees experienced higher prosthesis ownership than upper limb amputees. Positive associated with higher prosthesis ownership was a younger age, a longer

	Intervention: Survey	Secondary: Prosthesis use	length of the residual limb, longer time since amputation and a longer prosthetic use.
	Comparison: Non		
	Methodological notes Funding source: Research was supported by Deutsche Forschungsgemeinschaft, an EFIC Grünenthal Grant and an ERC Advenced Grant. COI declared (yes/no): Yes, no conflict was declared. Study Quality: High Publication bias: n/a Number of references: 67 Notes: Primary outcome was not prosthesis use, but the analysis showed relevant results in terms of it, which are relevant to our PICO question. Limits:		

5.1.4. Sensory discrimination training

PICO question	Does sensory discrimination training (SDT) lead to a detectable pain reduction in patients with phantom pain of any cause compared to usual care or placebo?		
List of sources	**Evidence level**	**Study type**	
1 Sensory discrimination training for adults with chronic musculoskeletal pain: a systematic review.	2	Systematic Review	
Source	**P-I-C**	**Outcome**	**Results**
1 Graham A, Ryan CG, MacSween A, Alexanders J, Livadas N, Oatway S, Atkinson G, Martin DJ. Sensory discrimination training for adults with chronic musculoskeletal pain: a systematic review. Physiother Theory Pract. 2022 Sep; 38(9):1107-1125. doi: 10.1080/09593985.2020.1830455. Epub 2020 Oct 20. PMID: 33078667.	Population: 18 adult amputees with PLP	Primary: Pain intensity using West-Haven Yale Multi-Purpose Inventory (WHYMPI) to record pain intensity (0-6, 0 = no pain, 6 = very intense pain)	There was very low-quality evidence from two studies supporting the efficacy of SDT for PLP. Given the high risk of bias within the included studies, no firm clinical recommendations can be made. GRADE rated recommendations show all studies to be of very low certainty (or quality) of evidence.
	Intervention: SDT	Secondary: Psychophysiological Assessment	
	Comparison: Standard care or residual limb massage		
	Methodological notes Funding source: industry COI declared: No conflict of interest. Study Quality: low Publication bias: high Number of references: 76 Notes: Limits: quality of individual studies included, small studies with a high risk of bias.		

5.1.5. Virtual reality/Augmented reality

PICO question	Does Virtual Reality / Augmented Reality lead to a detectable pain reduction in patients with phantom pain of any cause compared to usual care or placebo?

List of sources	**Evidence level**	**Study type**
1 Managing limb pain using virtual reality: a systematic review of clinical and experimental studies.	3	Systematic review of clinical and experimental studies
2 X-reality for phantom limb management for amputees: a systematic review and meta-analysis.	3	Systematic review and meta-analysis
3 Virtual and Augmented Reality-based Treatments for Phantom Limb Pain: A Systematic Review.	3	Systematic Review
4 Virtual and Augmented Reality in Management of Phantom Limb Pain: A Systematic Review.	3	Systematic Review
5 Use of virtual reality for the management of phantom limb pain: a systematic review.	3	Systematic Review
6 Efficacy of mirror therapy and virtual reality therapy in alleviating phantom limb pain: a meta-analysis and systematic review.	2	Systematic review and meta-analysis

Source	**P-I-C**	**Outcome**	**Results**
1 Wittkopf PG, Lloyd DM, Johnson MI. Managing limb pain using virtual reality: a systematic review of clinical and experimental studies. Disabil Rehabil. 2019 Dec; 41(26):3103-3117. doi: 10.1080/09638288.2018.1485183. Epub 2018 Sep 5. PMID: 30182760.	Population: 168 Participants with PLP, CRPS or neuropathic pain	Primary: Pain	Randomized controlled clinical trials showed no significant difference between intervention and control groups for pain intensity. Clinical studies with a single group pre-test post-test design showed a reduction in pain after intervention.
	Intervention: virtual representation of body parts	Secondary: embodiment of the virtual body part	
	Comparison: Motor imagery / Mirror Therapy		
	Methodological notes Funding source: internal COI declared: The authors have no conflicts of interest relevant to the contents of this article. Study Quality: ok Publication bias: low risk of bias associated with random sequence generation and incomplete outcome data; unclear risk of bias associated with allocation concealment and blinding of participants or outcome assessor; and high risk of bias associated with an absence of sample size calculation Number of references: 60 Notes: The two RCTs investigated the treatment effects in CRPS, no RCT on PLP Limits: None of the included studies provided a sample size calculation, small sample sizes and often without suitable controls, lack of blinding		

Reference	**P-I-C**	**Outcome**	**Results**

<table>
<tr><td rowspan="4">2 Cheung, J. C. W., Cheung, D. S. K., Ni, M., Chen, K. W., Mao, Y. J., Feng, L., ... & Leung, A. K. L. (2023). X-reality for phantom limb management for amputees: a systematic review and meta-analysis. Engineered Regeneration, 4(2), 134-151.</td><td>Population:
118 amputees</td><td>Primary:
Pain intensity</td><td rowspan="3">Overall, the X-reality interventions reduced the pain level of the amputees (mean difference: -2.30, 95% CI, -3.38 to -1.22), especially the virtual reality subgroup (mean difference: -2.83, 95% CI, -4.43 to -1.22). However, there were substantial heterogeneity and partially explained by the subgroup analysis on publication year. The strength of evidence was limited by case reports and case series in this review. […] The studies examined were all case studies and case series, with the exception of one randomised controlled clinical study by Rothangel et al. (2018). This RCT did not show any superiority of AR therapy over sensorimotor training.</td></tr>
<tr><td>Intervention:
VR
AT
Mixed Reality</td><td>Secondary:
Embodiment, QoL, Functioning, Depression, Anxiety</td></tr>
<tr><td>Comparison:
No treatment
MT
Sensomotor exercise</td><td></td></tr>
<tr><td colspan="3">Methodological notes
Funding source: internal/public
COI declared: The authors have no conflicts of interest relevant to the contents of this article.
Study Quality: low
Publication bias: “We did not assess the publication bias because of the presence of substantial heterogeneity.”
Number of references: 129
Notes: The studies examined were all case studies and case series, with the exception of one randomised controlled clinical study by Rothangel et al. (2018). This RCT did not show any superiority of AR therapy over sensorimotor training.
Limits: only English-written articles, exclusion of studies that mixed amputees with patients of other pathologies, imputation of standard error for single subject case reports, heterogeneity, mixed study design, ambiguity and confusion to distinguish between virtual reality, augmented reality, and mixed reality.</td></tr>
<tr><th>Reference</th><th>P-I-C</th><th>Outcome</th><th>Results</th></tr>
<tr><td rowspan="4">3 Vassantachart AY, Yeo E, Chau B. Virtual and Augmented Reality-based Treatments for Phantom Limb Pain: A Systematic Review. Innov Clin Neurosci. 2022 Oct-Dec; 19(10-12):48-57. PMID: 36591552; PMCID: PMC9776775.</td><td>Population:
Amputees or patient with brachial plexus avulsion</td><td>Primary:
PLP intensity</td><td rowspan="3">Six studies reported decreased PLP after AR/VR treatments, of which four reported significant reductions. One study reported a reduction in PLP with no significant difference from control conditions. […] Twelve studies reported decreased PLP after AR/VR treatments, of which eight reported significant reductions. One study found no change in PLP, compared to baseline.
While AR/VR systems and methodology vary widely in the available literature, there continues to be evidence that AR/VR therapies are a promising and relatively safe treatment to reduce PLP</td></tr>
<tr><td>Intervention:
VR/AR</td><td>Secondary:</td></tr>
<tr><td>Comparison:
Sham-VR
MT</td><td></td></tr>
<tr><td colspan="3">Methodological notes
Funding source: No funding was provided for this study.
COI declared (yes/no): The authors have no conflicts of interest relevant to the contents of this article.
Study Quality: One study was an unblinded RCT, with a PEDro Scale score of 8, and another study was a single-blinded RCxT, with a PEDro Scale score of 8. Three studies were comparative case series, with an average MINORS score of 17.3.</td></tr>
</table>

	Thirteen studies were noncomparative case series, with an average MINORS score of 10.8 and two studies were case reports with an average MINORS score of 8. Publication bias: low Number of references: 40 Notes: The studies gathered in the 2017 literature review by Dunn et al were included in this systematic review. Limits: Heterogeneity in methodologies, small sample sizes, only 2 RCTs		
Reference	**P-I-C**	**Outcome**	**Results**
4 Eldaly AS, Avila FR, Torres-Guzman RA, Maita KC, Garcia JP, Serrano LP, Emam OS, Forte AJ. Virtual and Augmented Reality in Management of Phantom Limb Pain: A Systematic Review. Hand (N Y). 2022 Nov 5:15589447221130093. doi: 10.1177/15589447221130093. Epub ahead of print. PMID: 36341580.	Population: Amputees or patient with brachial plexus avulsion	Primary: PLP intensity	All the studies reported improvement of PLP on one or more of pain scales after one or more sessions of VR or AR. Despite the promising results reported by literature, we cannot recommend using VR or AR for PLP. Most of the studies are of poor design and have limited sample size with high bias levels. Therefore, no substantial evidence can be derived from them.
	Intervention: VR and AR	Secondary: impact of health on quality of life; psychiatric effects of the intervention	
	Comparison: MT Sensomotor exercise		
	Methodological notes Funding source (public/industry/internal): The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported in part by the Mayo Clinic Center for Regenerative Medicine COI declared (yes/no): The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Study Quality: According to Cochrane Back Review Group Qualitative Methods, this systematic review reports limited evidence on the effectiveness of VR and AR in reducing PLP as we included only one good-quality RCT and multiple fair to poor quality before-after (pre-post) studies with no control group. Publication bias: bias of misinterpreting data and results, and bias in the study selection process Number of references: 40 Notes: RCT did not recommend VR Limits: heterogeneity, only 1 study was a good-quality RCT, while the rest were non-randomized, uncontrolled trials of fair to poor quality. These factors limited the evidence concluded from these studies.		
Reference	**P-I-C**	**Outcome**	**Results**
5 Hali K, Manzo MA, Koucheki R, Wunder JS, Jenkinson RJ, Mayo AL, Ferguson PC, Lex JR. Use of virtual reality for the management of phantom limb pain: a systematic review. Disabil Rehabil. 2024 Feb; 46(4):629-636. doi: 10.1080/09638288.2023.2172222. Epub 2023 Feb 1. PMID: 36724203.	Population: 109 adult amputees	Primary: PLP intensity	The literature reports a decrease in PLP following VR sessions. VR is currently being recommended as a treatment option for PLP due to its low adverse event rate and the expert consensus of its utility. The combination of VR with tactile stimulation has a larger beneficial effect on PLP compared with VR alone. VR has the potential to be an effective treatment modality for PLP following amputation.
	Intervention: Virtual Reality	Secondary: No	
	Comparison: No comparison		
	Methodological notes Funding source (public/industry/internal): No funding. COI declared (yes/no): The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Study Quality: moderate (MINORS-Score 15,7/24 und 10,7/16) Publication bias: n.a. Number of references: 42		

	Notes: No RCT. Limits: small sample sizes, no control group, no RCT, low quality of the studies, heterogeneity in subject populations and intervention types, short-term measures, 89% males,		
Reference	**P-I-C**	**Outcome**	**Results**
6 Rajendram C, Ken-Dror G, Han T, Sharma P. Efficacy of mirror therapy and virtual reality therapy in alleviating phantom limb pain: a meta-analysis and systematic review. BMJ Mil Health. 2022 Apr; 168(2):173-177. doi: 10.1136/bmjmilitary-2021-002018. Epub 2022 Jan 18. PMID: 35042760.	Population: 86 adult amputees	Primary: PLP intensity	A total of 15 studies met our search criteria; they consisted of eight mirror therapy with 214 participants and seven VR including 86 participants, totalling 300 participants. Mean age ranged from 36 to 63 years, 77% male, of which 61% were lower body amputees. Both led to a VAS reduction (mirror therapy mean reduction VAS score was 2.54, 95% CI 1.42 to 3.66; p<0.001; VR 2.24, 95% CI 1.28 to 3.20; p<0.001). There was no statistically significant difference in pain alleviation between mirror therapy and VR (p=0.69). Mirror therapy and VR are both equally efficacious in alleviating PLP, but neither is more effective than the other. However, due to small sample size and limited number of studies, factors such as gender, cause of amputation, site of limb loss or length of time from amputation, which may influence treatment success, could not be explored.
	Intervention: Virtual Reality	Secondary:	
	Comparison: No comparison		
	Methodological notes Funding source: no funding COI declared (yes/no): none declared. Study Quality: low Publication bias: high Number of references:29 Notes: The results are very contradictory and the supposedly randomised study by Cole et al from 2009 is not a randomised controlled trial but a case series. Limits: small sample sizes, no control group, one RCT, this RCT did not show any superiority of AR therapy over sensorimotor training, one randomized cross-over trial.		

5.1.6. Action observation

PICO question	Does Action Observation (AO) lead to a detectable pain reduction in patients with phantom pain of any cause compared to routine care or placebo?		
List of sources	**Evidence level**	**Study type**	
1 Decreasing phantom limb pain through observation of action and imagery: a case series.	4	single-case multiple baseline study	
Source	**P-I-C**	**Outcome**	**Results**
1 Beaumont G, Mercier C, Michon PE, Malouin F, Jackson PL. Decreasing phantom limb pain through observation of action and imagery: a case series. Pain Med. 2011 Feb; 12(2):289-99. doi: 10.1111/j.1526-4637.2010.01048.x. Epub 2011 Jan 28. PMID: 21276185.	Population: 7 Amputees with PLP	Primary: Pain (VAS)	Time series analysis showed that three participants rated their pain gradually and significantly lower during Intervention 1. During Intervention 2, additional changes in pain slopes were not significant. Four participants reported a reduction of pain greater than 30% from baseline to the end of Intervention 2, and only one maintained his gains after 6 months. Group analyses confirmed that average pain levels were lower after intervention than at baseline and had returned to baseline after 6 months. Social support, degree of functionality, and perception of control about their lives prior to the intervention correlated significantly with pain reduction.
	Intervention: 1: AO with therapist 2: AO homebased 3: AO + Motor imagery	Secondary: Imagery Rating of Videos	
	Comparison: No Comparison.		
	Methodological notes Funding source: public COI declared: The authors have no conflicts of interest Study Quality: very low Publication bias: no Number of references: 26 Notes: “The fact that this method could be used almost anytime and anywhere as it is a relatively simple and inexpensive method that patients learn quickly makes it a good potential adjunct to current treatment methods.” Limits: no control group, very small group, all patients were able to move their phantom limb		

5.1.7. Biofeedback training

PICO question	Does Biofeedback training lead to a detectable pain reduction in patients with phantom pain of any cause compared to usual care or placebo?

List of sources	**Evidence level**	**Study type**
1 Relieving phantom limb pain with multimodal sensory-motor training.	4	Case-series study
2 Training without Explicit Phantom Hand Movements and Hand-Like Visual Feedback to Modulate Pain: A Randomized Crossover Feasibility Trial.	4	Single-blind randomized Crossover Feasibility Trial
3 Leg Prosthesis With Somatosensory Feedback Reduces Phantom Limb Pain and Increases Functionality.	5	Within subject design after waiting period
4 Motor Control and Sensory Feedback Enhance Prosthesis Embodiment and Reduce Phantom Pain After Long-Term Hand Amputation.	5	Case study
5 Sensory feedback prosthesis reduces phantom limb pain: proof of a principle.	5	Within subjects design (repeated measures) after waiting period
6 The Feeling Prosthesis-Somatosensory Feedback from the Prosthesis Foot Reduces Phantom Limb Pain Dramatically.	5	Case study with waiting period

Source	**P-I-C**	**Outcome**	**Results**
1 De Nunzio AM, Schweisfurth MA, Ge N, Falla D, Hahne J, Gödecke K, Petzke F, Siebertz M, Dechent P, Weiss T, Flor H, Graimann B, Aszmann OC, Farina D. Relieving phantom limb pain with multimodal sensory-motor training. J Neural Eng. 2018 Dec;15(6):066022. doi: 10.1088/1741-2552/aae271. Epub 2018 Sep 19. PMID: 30229747.	Population: 1 0 upper-limb amputees	Primary: PLP intensity	The study results revealed a substantial reduction in phantom limb pain intensity, obtained with a new training protocol focused on improving phantom limb motor output using visual and tactile feedback from the stump muscular activity executed to move the phantom limb. A 32.1% reduction of PLP intensity was obtained at the follow-up (6 weeks after the end of the training, with an initial 21.6% reduction immediately at the end of the training) reaching clinical effectiveness for chronic pain reduction.
	Intervention: Intensive training on phantom-limb movement control and visual and tactile feedback, driven by muscular activity at the stump	Secondary: Expectancy and rationale credibility, MPI-D, SES, PainDetect, PCS, DASS-21, SF-36, and Satisfaction scale.	
	Comparison: n.a.		
	Methodological notes Funding source: This work was financially supported by the European Commission under the MYOSENS (FP7-PEOPLE-2011-IAPP-286208) project. COI declared: The authors have declared that no competing financial interests exist. Study Quality: high Publication bias: n.a. Number of references: 81 Notes: no RCT		

	Limits: small sample size, no control group, unspecific therapeutic effects

Reference	P-I-C	Outcome	Results
2 Yanagisawa T, Fukuma R, Seymour B, Tanaka M, Yamashita O, Hosomi K, Kishima H, Kamitani Y, Saitoh Y. Neurofeedback Training without Explicit Phantom Hand Movements and Hand-Like Visual Feedback to Modulate Pain: A Randomized Crossover Feasibility Trial. J Pain. 2022 Dec;23(12):2080-2091. doi: 10.1016/j.jpain.2022.07.009. Epub 2022 Aug 3. PMID: 35932992.	Population: 14 patients with PLP, 2 amputees and 14 patients with brachial plexus root avulsion	Primary: PLP intensity	The pain assessed by the visual analogue scale was significantly greater after contralateral training than after ipsilateral training. Classification accuracy of phantom hand movements significantly increased only after contralateral training (contralateral training, 35.3 ± 12.9; ipsilateral training, 27.8 ± 13.4; p = 0.012, paired Student's t-test). These results suggested that the proposed neurofeedback training changed phantom hand representation and modulated pain without explicit phantom hand movements or hand-like visual feedback, thus showing the relation between the phantom hand representations and pain.
	Intervention: First contralateral, then ipsilateral neurofeedback training	Secondary: Classification Accuracy of Phantom Hand Movements	
	Comparison: First ipsilateral then contralateral neurofeedback training		
	Methodological notes Funding source: Japan Agency for Medical Research and Development (AMED [grant no. JP19dm0307008]) and also in part by the Japan Science and Technology Agency's Core Research for Evolutional Science and Technology (JPMJCR18A5), Exploratory Research for Advanced Technology (JPMJER1801) and Moonshot R&D (JPMJMS2012); by Grants-in-Aid for Scientific Research from KAKENHI (JP17H06032, JP20H05705, JP18H04085, and JP18H05522); by AMED (19dm02070h0001, JP19dm0307103, and 19de0107001); and by the Mitsubishi Foundation. COI declared (yes/no): All authors declare that they have no actual or potential conflicts of interest. Study Quality: moderate Publication bias: n.a. Number of references: 39 Notes: The statistical analysis appears to be worth checking, the mean value comparisons are in the range of the standard deviations of the control group and we have doubts about a significant group difference. Limits: functional connectivity between bilateral sensorimotor activities, crossover design, one-time intervention		
Reference	**P-I-C**	**Outcome**	**Results**
3 Dietrich, C., Nehrdich, S., Seifert, S., Blume, K. R., Miltner, W. H. R., Hofmann, G. O., & Weiss, T. (2018). Leg Prosthesis With Somatosensory Feedback Reduces Phantom Limb Pain and Increases Functionality. Frontiers in neurology, 9, 270. https://doi.org/10.3389/fneur.2018.00270	Population: 14 unilateral lower limb amputees (5 females, mean age = 56.3 years ± 11.6, range: 27–76). Patients were recruited through advertisements and from patient pools of the	Phantom characteristics and pain including core dimensions, the German Version of the McGill Pain Questionnaire, scores on physical functioning	Two weeks of training with such a feedback prosthesis reduced PLP, increased the functional use of the prosthesis, and increased patients' satisfaction with prosthesis use. We found a significant overall reduction of PLP during the course of the training period. Most

	German Social Accident Insurance	according to the German Version of the West Haven-Yale Multidimensional Pain Inventory, the German Version of the Pain Catastrophizing Scale, scores on emotional functioning: the German Version of the Becks Depression Inventory, BDI-II, the State-Trait Anxiety Inventory, and the German version of the Health Survey (SF-36).	patients reported lower PLP intensities at the end of the day while before training they have usually experienced maximal PLP intensities. Furthermore, patients also reported larger walking distances and more stable walking and better posture control while walking on and across a bumpy or soft ground. After training, the majority of participants (9/14) preferred such a feedback system over no feedback.
	Intervention: daily training of 2h 5x/week over a period of 2 weeks. At the beginning of each training day, electrodes for electrocutaneous SAF were attached to the residual leg in the middle of the thigh above the liner.	Secondary: Pain diary	
	Comparison: Waiting periode		
	Methodological notes Funding source: This work was supported by grants from the German Social Accident Insurance (DGUV-FR145 and FR196). DGUV neither did not influence on study goals nor on study design; i.e., authors are fully responsible for goals and design. COI declared (yes/no): Yes, no conflicts declared. Study Quality: moderate Publication bias: n.a. Number of references: 73 Notes: Study design: The study used a within-subjects design. The study included a baseline assessment followed by a 2-week waiting period, a pretraining assessment (Pre), a 2-week training period, and a posttraining assessment (Post) Limits: No randomization, probably selection bias, low number of participants		
Reference	**P-I-C**	**Outcome**	**Results**
4 Page DM, George JA, Kluger DT, Duncan C, Wendelken S, Davis T, Hutchinson DT and Clark GA (2018) Motor Control and Sensory Feedback Enhance Prosthesis Embodiment and Reduce Phantom Pain After Long-Term Hand Amputation.	Population: 57-year-old, left-hand-dominant male, whose left foot and left forearm had been	Primary: Prosthesis embodiment	there was a significant level of embodiment of the physical prosthetic limb after open-loop motor control of the prosthesis (i.e., without sensory

Front. Hum. Neurosci. 12:352. doi: 10.3389/fnhum.2018.00352	amputated 13 years prior, after an electrocution injury.		feedback), open-loop sensation from the prosthesis (i.e., without motor control), and closed-loop control of the prosthesis (i.e., motor control with sensory feedback). There was also a statistically significant reduction in reported phantom pain after experimental sessions that included open-loop nerve microstimulation, open-loop prosthesis motor control, or closed-loop prosthesis motor control. The closed-loop condition provided no additional significant improvements in phantom pain reduction or prosthesis embodiment relative to the open-loop sensory condition or the open-loop motor condition.
	Intervention: Use of closed-loop physical prosthesis control with USEA-evoked sensory feedback in one human amputee	Secondary: Phantom pain reduction	
	Comparison: Non		
	Methodological notes Funding source: Hand Proprioception and Touch Interfaces (HAPTIX) program administered by the Biological Technologies Office (BTO) of the Defense Advanced Research Projects Agency (DARPA), through the Space and Naval Warfare Systems Center, Contract No. N66001-15-C-4017. Additional sponsorship was provided by the National Science Foundation (NSF) through grant no. NSF ECCS-1533649 COI declared (yes/no): One author had no conflicts. Six authors declared a conflict of interests because of patents (listed in publication) Study Quality: Good Publication bias: n.a. Number of references: 79 Notes: non Limits: Probably selection bias		
Reference	**P-I-C**	**Outcome**	**Results**
5 Dietrich, C., Walter-Walsh, K., Preissler, S., Hofmann, G. O., Witte, O. W., Miltner, W. H., & Weiss, T. (2012). Sensory feedback prosthesis reduces phantom limb pain: proof of a principle. Neuroscience letters, 507(2), 97–100. https://doi.org/10.1016/j.neulet.2011.10.068	Population: Eight amputees were included in the study. Inclusion criteria were a transradial amputation with no plexus avulsion and the presence of phantom limb pain.	Primary: Functionality (Goal attainment scaling), current intensity of PLP (VAS), and experienced change of PLP (CPLP)	Patients reported that they successfully mastered their target motor tasks that had been expressed at the beginning of training (Mdn = 75%, Z = 2.27, $p < 0.05$). All patients reported a reduction of PLP intensity on the CPLP (M=47.75%, SD =32.02%, $t(7) = -4.22$, $p < 0.05$). Compared to the waiting period it shows a significant difference (M= 17.95%, SD=13.62%, $t(4) = 2.95$, $p < 0.05$).
	Intervention: Daily prosthesis training for 10 consecutive working days. Each training session lasted 3.5 h, with a 20 min break.	Secondary:	

	Comparison: Non		
	Methodological notes Funding source: This work was supported by the German Social Accident Insurance DGUV FR-145 (Deutsche Gesetzliche Unfallversicherung). COI declared (yes/no): Yes. No conflicts Study Quality: Good Publication bias: n.a. Number of references: 46		
Reference	**P-I-C**	**Outcome**	**Results**
6 Preißler, S., Dietrich, C., Seifert, S., Hofmann, G. O., Miltner, W. H. R., & Weiss, T. (2018). The Feeling Prosthesis-Somatosensory Feedback from the Prosthesis Foot Reduces Phantom Limb Pain Dramatically. Pain medicine (Malden, Mass.), 19(8), 1698–1700. https://doi.org/10.1093/pm/pnx295	Population: 54-year-old man who suffered from PLP in his left amputated foot.	Primary: PLP intensity (VAS), Pain dairy	Analysis of the VAS scores from the pain diary showed a significant reduction of PLP. Compared with the untreated baseline period, HT reported lower daytime and nighttime PLP. Prior to the training, HT's mean PLP was 1.19 in the morning, 2.85 at noon, and 3.85 in the evening, with an average PLP score of 2.63. An ANOVA revealed significantly lower PLP scores at the end of the training period and at the follow-up period compared with the waiting period ($F(2, 71)=65.18$, $P<0.001$), with no difference between the end of training and the follow-up period.
	Intervention: To provide Somato-sensory feedback, three pressure sensors were attached to the sole of the prosthesis foot (heel, middle outer surface, and bunion). Somato-sensory feedback about pressure at these locations was provided to the stump.	Secondary:	
	Comparison: Waiting period		
	Methodological notes Funding source: The German Social Accident Insurance founded this study (DGUV-FR145 and FR196). DGUV did not have any influence on the goals or design of the current study (i.e., the authors are fully responsible for goals and design). COI declared (yes/no): Yes, no conflict declared. Study Quality: moderate Publication bias: n.a. Number of references: 9		

5.1.8. Electromagnetic shielding

PICO question	Does “electromagnetic shielding” lead to a detectable pain reduction in patients with phantom pain of any cause compared to usual care or placebo?	
List of sources	**Evidence level**	**Study type**
1 The effect of electromagnetic shielding on phantom limb pain: A placebo-controlled double-blind crossover trial.	2	placebo-controlled double-blind crossover trial
2 Management of phantom pain with a textile, electromagnetically-acting stump liner	2	randomized, double-blind, crossover study

Source	P-I-C	Outcome	Results
1 Fisher K, Oliver S, Sedki I, Hanspal R. The effect of electromagnetic shielding on phantom limb pain: A placebo-controlled double-blind crossover trial. Prosthet Orthot Int. 2016 Jun;40(3):350-6. doi: 10.1177/0309364614568409. Epub 2015 Feb 25. PMID: 25716957.	Population: 20 adult Participants with PLP	Primary: Change in mean and maximum PLP severity assessed by NRS (0-10)	The remaining data showed that maximum pain and wellbeing were improved from baseline under verum but not placebo. More participants improved on all variables with verum than placebo. There were no statistically significant differences between VL and PL on any variables (p>0.05).
	Intervention: Electromagnetic shielding Liner	Secondary: Well-being, disability, wearing time	
	Comparison: Liner		
	Methodological notes Funding source (public/industry/internal): None COI declared: The authors have no conflicts of interest. Study Quality: low Publication bias: high risk of bias Number of references: 23 Limits: skin problems in response to the silicon encountered by more than a quarter of our sample population, the study ended up underpowered. Carry over effect. Small group. 33% dropouts. Unclear mechanism of the effect.		

Source	P-I-C	Outcome	Results
2 Kern U, Altkemper B, Kohl M. Management of phantom pain with a textile, electromagnetically-acting stump liner: a randomized, double-blind, crossover study. J Pain Symptom Manage. 2006 Oct;32(4):352-60. doi: 10.1016/j.jpainsymman.2006.04.006. PMID: 17000352.	Population: 30 adult Participants with PLP	Primary: Change in PLP assessed by NRS (0-10)	Our study reveals a significant reduction in both average and maximum intensity of phantom pain, and a significant increase in well-being, when a stump silicon stocking with electromagnetically shielding properties was used versus a placebo.
	Intervention: Electromagnetic shielding Liner	Secondary: Well-being, Sleep	
	Comparison: Liner		
	Methodological notes Funding source (public/industry/internal): industry COI declared: The authors have no conflicts of interest Study Quality: low Publication bias: high risk Number of references: 40 Notes: 2006, Median, poor information about the statistical analysis, regression to the mean? Limits: small sample size		

5.1.9. Exercise / phantom exercise training

PICO question	Does (phantom) exercise lead to a detectable pain reduction in patients with phantom pain of any cause compared to usual care or placebo?

List of sources	Evidence level	Study type
1 Effectiveness of phantom exercises for phantom limb pain: a pilot study.	2	RCT
2 Effects of phantom exercises on pain, mobility, and quality of life among lower limb amputees; a randomized controlled trial.	2	RCT

Source	P-I-C	Outcome	Results
1 Ulger O, Topuz S, Bayramlar K, Sener G, Erbahçeci F. Effectiveness of phantom exercises for phantom limb pain: a pilot study. J Rehabil Med. 2009 Jun;41(7):582-4. doi: 10.2340/16501977-0380. PMID: 19543671.	Population: 20 traumatic amputees with acute PLP	Primary: Pain (VAS)	Pain intensity decreased in all subjects after 4 weeks of treatment in both groups. According to the visual analogue scale scores at the end of 4 weeks, the phantom exercises group differed significantly from the general exercise group ($p < 0.05$).
	Intervention: phantom exercises and prosthetic training	Secondary: Phantom sensation	
	Comparison: routine prosthetic training and a general exercise		
	Methodological notes Funding source (public/industry/internal): no information COI declared (yes/no): no information Study Quality: ok Publication bias: no Number of references: 15 Notes: 6 month-follow-up without results: "*When the patients were telephoned 2 months after discharge, they reported that they performed phantom exercises during PLP and experienced a decrease in the frequency of PLP*." Limits: Only acute PLP. Missing data for 6 month follow up.		

Reference	P-I-C	Outcome	Results
2 Zaheer A, Malik AN, Masood T, Fatima S. Effects of phantom exercises on pain, mobility, and quality of life among lower limb amputees; a randomized controlled trial. BMC Neurol. 2021 Oct 27; 21(1):416. doi: 10.1186/s12883-021-02441-z. PMID: 34706654; PMCID: PMC8554869.	Population: 24 unilateral lower limb amputees	Primary: Pain	The Addition of phantom exercises resulted in significantly better pain management in lower limb amputees treated with mirror therapy and routine physiotherapy. After the intervention, the pain (VAS score) was significantly lower in the experimental group (p=0.003). Similarly, the experimental group demonstrated a significantly better score in the "bodily pain" domain of SF-36 (p=0.012). Both groups significantly (p<0.05) improved in other domains of SF-36 and ambulatory potential with no significant (p>0.05) between-group
	Intervention: mirror therapy, conventional physical therapy and additional phantom exercises	Secondary: Mobility Quality of Life	
	Comparison:		

	mirror therapy and conventional physical therapy		differences.
	Methodological notes Funding source: internal COI declared: The authors have no conflicts of interest. Study Quality: high Publication bias: no Number of references: 34 Notes: After 4 weeks of therapy, a significant reduction in pain was observed in both groups compared to baseline; significant changes between the groups could only be demonstrated after 4 weeks in favour of the phantom exercise group. Limits: small sample size, no statistical analysis of medication use and reason/localisation of amputation.		

5.1.10. Intermanual transfer

PICO question	Does intermanual transfer lead to a detectable pain reduction in patients with PLP of any cause compared to usual care or placebo?	
List of sources	**Evidence level**	**Study type**
No Results		

5.1.11. Laterality recognition

PICO question	Does laterality recognition lead to a detectable pain reduction in patients with phantom pain of any cause compared to routine care or placebo?

List of sources	Evidence level	Study type
1 Body representation among adults with phantom limb pain: Results from a foot identification task.	4	Clinical trial

Source	P-I-C	Outcome	Results
Beisheim-Ryan EH, Pohlig RT, Medina J, Hicks GE, Sions JM. Body representation among adults with phantom limb pain: Results from a foot identification task. Eur J Pain. 2022 Jan;26(1):255-269. doi: 10.1002/ejp.1860. Epub 2021 Sep 17. PMID: 34490685; PMCID: PMC8671232.	Population: n = 41 adults with PLP n = 27 Pain-Free peers with lower limb loss n = 39 Controls with intact limbs (n=107)	Primary: Performance and response time of left–right discrimination	Adults with PLP demonstrated slower and less accurate performance as compared to Controls with intact limbs (p = 0.018) but performed similarly to Pain-Free peers with LLL (p = 0.394). Significant three-way interactions of group, view and angle indicated between-group differences were greatest for dorsal-view images, but smaller and angle-dependent for plantar-view images. While all groups demonstrated significant response time improvements across blocks, improvements were greatest among adults with PLP, who also reported significant reductions in pain intensity.
	Intervention: Participants judged whether randomized images depicted left or right feet (i.e. left–right discrimination) as quickly as possible without limb movement.	Secondary: PLP Phantom limb sensation ADL	
	Comparison: Pain-Free peers with and without lower limb loss		
	Methodological notes Funding source: public COI declared : The authors have no conflicts of interest. Study Quality: OK Publication bias: Number of references: 62 Notes: secondary outcome Limits: No comparison with usual care, pain is a secondary outcome, no investigation of the analgesic efficacy, pain-reducing effects may be non-specific, e.g. due to study participation.		

5.1.12. Motor imagery

PICO question	Does motor imagery lead to a detectable pain reduction in patients with phantom pain of any cause compared to routine care or placebo?		
List of sources	**Evidence level**	**Study type**	
1 The Efficacy of Movement Representation Techniques for Treatment of Limb Pain - A Systematic Review and Meta-Analysis.	2	Systematic Review and Meta-Analysis	
Reference	**P-I-C**	**Outcome**	**Results**
1 Thieme H, Morkisch N, Rietz C, Dohle C, Borgetto B. The Efficacy of Movement Representation Techniques for Treatment of Limb Pain--A Systematic Review and Meta-Analysis. J Pain. 2016 Feb;17(2):167-80. doi: 10.1016/j.jpain.2015.10.015. Epub 2015 Nov 6. PMID: 26552501.	Population: Adults with limb pain Excluded: cancer pain, Patients with pain distribution to other areas	Primary: Pain intensity	[…] To date, there is no evidence for a pain reducing effect of movement representation techniques in patients with phantom limb pain and poststroke pain other than complex regional pain syndrome.
	Intervention: Movement representation techniques	Secondary: Quality of life, disability, adverse events	
	Comparison: No treatment group, usual or standard practice, or any other control interventions including placebo or sham therapy		
	Methodological notes Funding source: public COI declared: No conflict of interest. Study Quality: low Publication bias: no Number of references: 63 Notes: Only 3 of the included studies focus on PLP, these studies are described as qualitatively limited. Limits: possibility of missing relevant publications, small sample sizes and differences in therapy delivery between studies		

5.1.13. (Progressive residual limb) Muscle relaxation (techniques)

PICO question	Does (progressive residual limb) muscle relaxation lead to a detectable pain reduction in patients with phantom pain of any cause compared to usual care or placebo?

List of sources	**Evidence level**	**Study type**
1 Efficacy of progressive muscle relaxation, mental imagery, and phantom exercise training on phantom limb: a randomized controlled trial.	2	Randomized controlled prospective trial with 2 parallel groups.

Source	**P-I-C**	**Outcome**	**Results**
1 Brunelli S, Morone G, Iosa M, Ciotti C, De Giorgi R, Foti C, Traballesi M. Efficacy of progressive muscle relaxation, mental imagery, and phantom exercise training on phantom limb: a randomized controlled trial. Arch Phys Med Rehabil. 2015 Feb;96(2):181-7. doi: 10.1016/j.apmr.2014.09.035. Epub 2014 Oct 23. PMID: 25450123.	Population: Subjects with unilateral lower limb amputation with phantom limb pain (PLP) and/or phantom limb sensation (PLS)	Primary: The Prosthesis Evaluation Questionnaire and the Brief Pain Inventory were used to evaluate changes over time in different aspects (intensity, rate, duration, and bother) of PLS and PLP.	The experimental group showed a significant decrease over time in all the Prosthesis Evaluation Questionnaire domains (in terms of both PLS and PLP; P<.04 for both) and the Brief Pain Inventory (P<.03). No statistically significant changes were observed in the control group. Between-group analyses showed a significant reduction in intensity (average and worst pain) and bother of PLP and rate and bother of PLS at follow-up evaluation, 1 month after the end of the treatment.
	Intervention: combined training of progressive muscle relaxation, mental imagery, and phantom exercises 2 times/wk for 4 weeks	Secondary: n.a.	
	Comparison: same amount of physical therapy, exercise program		
	Methodological notes Funding source: no information COI declared: No conflict of interest. Study Quality: high Publication bias: no Number of references: 55 Notes: A combination of PMR, mental imagery, and modified phantom exercises was effective in reducing the intensity, rate, and bother of PLP and PLS in persons with amputation 1 month after the intervention. Combination of different effective methods (MI, MT) does not allow for a definitive statement with regard to relaxation techniques. Limits: The study population had a high proportion of amputations due to diabetes and peripheral vascular disease, rather than nonvascular disease. This heterogeneity means that participants in the present study may have different mechanisms underlying their pain than might persons with other amputation ethology.		

5.1.14. (Residual limb) massage

PICO question	Does (residual limb) massage lead to a detectable pain reduction in patients with PLP of any cause compared to usual care or placebo?	
List of sources	**Evidence level**	**Study type**
No Results		

5.1.15. Residual limb bandaging

PICO question	Does residual limb bandaging lead to a detectable pain reduction in patients with PLP of any cause compared to usual care or placebo?	
List of sources	**Evidence level**	**Study type**
No Results		

5.1.16. TENS*

PICO question:	Does TENS lead to a detectable pain reduction of 30 % in patients with phantom pain of any cause compared to usual care or placebo?		
List of sources	**Evidence level**	**Study type**	
1 Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults.	n.a.	Systematic Review	
Source	**P-I-C**	**Outcome**	**Results**
1 Johnson MI, Mulvey MR, Bagnall A-M. Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD007264. DOI: 10.1002/14651858.CD007264.pub3.	Population: Adult participants (16 years or above) with any limb amputation resulting in any type of pain in a phantom or stump, or both.	Primary: Patient-reported pain	In the original review there were no RCTs that examined the effectiveness of TENS for the treatment of phantom pain and stump pain in adults. For this update, we did not identify any additional RCTs for inclusion.
	Intervention: surface electrical nerve stimulation (TENS)	Secondary: Any other related pain, PLS, satisfaction, ADLs, ROM, Qol, Anxiety/depression, Use of pain coping strategies, Sleep, Analgesics, Hospital attendance, adverse effects	
	Comparison: • TENS versus no treatment controls. • TENS versus sham controls. • TENS versus a pharmacological intervention. • TENS versus a non-pharmacological intervention.		
	Methodological notes Funding source: public COI declared: No conflict of interest. Study Quality: high Publication bias: There were no trials included in this review so risk of bias could not be evaluated. Number of references:66 Notes/Limits: There were no trials included in this review so risk of bias could not be evaluated.		

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