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REVIEW

A review of the management of phantom limb pain: challenges and solutions

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Background: Phantom limb pain (PLP) occurs in 50% and 80% of amputees. Although it is often classified as a neuropathic pain, few of the large-scale trials of treatments for neuropathic pain included sufficient numbers of PLP sufferers to have confidence that they are effective in this condition. Many therapies have been administered to amputees with PLP over the years; however, as of yet, there appears to be no first-line treatment.

Objectives: To comprehensively review the literature on treatment modalities for PLP and to identify the challenges currently faced by clinicians dealing with this pain.

Method: MEDLINE, EMBASE, CINAHL, British Nursing Index, Cochrane and psycINFO databases were searched using "Phantom limb" initially as a MeSH term to identify treatments that had been tried. Then, a secondary search combining phantom limb with each treatment was performed to find papers specific to each therapy. Each paper was assessed for its research strength using the GRADE system.

Results: Thirty-eight therapies were identified. Overall, the quality of evidence was low. There was one high-quality study which used repetitive transcutaneous magnetic stimulation and found a statistical reduction in pain at day 15 but no difference at day 30. Significant results from single studies of moderate level quality were available for gabapentin, ketamine and morphine; however, there was a risk of bias in these papers. Mirror therapy and associated techniques were assessed through two systematic reviews, which conclude that there is insufficient evidence to support their use.

Conclusion: No decisions can be made for the first-line management of PLP, as the level of evidence is too low. Robust studies on homogeneous populations, an understanding of what amputees consider a meaningful reduction in PLP and agreement of whether pain intensity is the legitimate therapeutic target are urgently required.

Keywords: phantom limb pain, review, treatment, pain

Introduction

Phantom limb pain (PLP) occurs in 50%–80% of limb amputees[1–4] and is known to be highly fluctuant.[1,5] As PLP is associated with deafferentation and is known to be associated with cortical reorganization[6] of the somatosensory system, it is often classified as a neuropathic pain; however, no large neuropathic pain drug trials included sufficient number of people with PLP to have confidence that they are effective in this condition.[7] This is reinforced by the updated Cochrane reviews for the use of amitriptyline, carbamazepine, gabapentin, pregabalin and lamotrigine in treating neuropathic pain.[8–12]

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In 1980, Sherman identified that 43 treatments had been used to control PLP[13] and since that time, multiple drugs, surgery and complementary therapies have been added to the list. According to a recent Cochrane review of pharmacologic interventions for PLP, there is inconclusive evidence for any single therapy.[14]

For a while, focus turned toward the potential to prevent rather than treat PLP by aggressively controlling preamputation or immediate postamputation pain.[15–17] Results from these studies have been equivocal with the stronger studies favoring no effect.[18] To add to the confusion, treatments used for acute PLP have often been commenced preemptively and it can be difficult to resolve these from studies on established PLP. More recently, treatments aimed at reversing cortical reorganizations,[19] such as mirror therapy and associated treatments, have been the center of attention.[20]

This review has, therefore, explored the management of established PLP, with a remit to be as broad as possible to give practitioners all relevant data about how to treat this perplexing and intractable condition. It is hoped that by including all treatments rather than selecting them by method and quality, clinicians will be able to evaluate their treatment strategies against rumor and speculation. Additionally, our ambition is, through the appraisal of the literature, to identify the challenges that practitioners have when treating people with PLP and how best to resolve them.

Method

This should not be regarded as a systematic review; however, approaches consistent with systematic reviews have been utilized. In line with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) criteria, the search was designed to identify treatments/therapies that improve one or more of the following outcomes: pain, function, global impression of change and lower side effects.[18] MEDLINE, EMBASE, CINAHL, British Nursing Index, Cochrane and psycINFO were searched in April 2017 and as far back as their dates would allow using "Phantom limb" initially as a MeSH term to identify treatments that had been used previously. Then, a secondary search combining PLP with each treatment was undertaken to find papers specific to each therapy. The search strategy is outlined in Table 1.

Table 1 Search strategy

Step	Action
1	"Phantom Limb" searched as MeSH term
2	Titles searched for treatments
3	List of treatments identified
4	Second database search. "Phantom limb" combined with each treatment (included generic medication group and individual drugs from that group, i.e., "antidepressive agents" and "amitriptyline")
5	Excluded non-English papers or if full text was unavailable
6	Excluded all papers that were not treatment evaluations
7	Reference lists of papers scanned for any papers not previously identified

Inclusion/exclusion criteria

Only human studies for established PLP were included. Studies treating PLP in the acute postoperative phase were excluded as it is very difficult to delineate PLP from stump pain (SP) in this period. All levels of evidence from single case studies to randomized controlled trials (RCTs) were included. A modified PRISMA flow diagram for antidepressive agents as an example for the process for each treatment is shown in Table 2.

Table 2 Example of search on MEDLINE for antidepressive agents

MeSH term	Hits	Boolean operator "And"	Inclusion/ exclusion applied
Phantom limb	1725	8	2
Amitriptyline	6412		
Phantom limb	1725	2	2
Doxepin	758		
Phantom limb	1725	0	0
Nortriptyline	2133		
Phantom limb	1725	14	1
Antidepressive agents	39,073		
			Total=5

Quality assessment

The GRADE system was utilized[21] to assess the quality of each paper. GRADE has been said to overcome some of the arbitrariness of other categorization systems which weigh particular research methods, even when there may be significant biases present in individual studies using those methods. GRADE utilizes four levels of quality, High, Moderate, Low and Very Low, and takes account of limitations, inconsistencies, directness and imprecision of the study for the topic being investigated. The quality assessment criteria used are included in Table 3. One of the main issues encountered within the quality assessment process was the fact that many papers that would normally have been assessed as being high quality used mixed samples, that is, upper (major or minor) and lower limb (major or minor) amputees, or included pain reduction of PLP and SP within the outcomes. If it was not possible to extract the PLP patients from the pooled data, the quality assessment was downgraded accordingly. All

Table 3 Evidence is assessed using four levels of quality as defined by the GRADE system

GRADE score	Description	Agreed criteria within studies used for this comprehensive review
High quality	Further research is very unlikely to change our confidence in the estimate of effect	Randomization Control group Active placebo Homogenous sample of amputees PLP sole outcome or able to be clearly differentiated from other outcomes, for example, SP Sample size decided by power calculation or at least 50 (25 in cross-over studies) to enable comparative statistics to be performed
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate	Randomization Control group Inactive placebo Heterogeneous sample of amputees PLP sole outcome or able to be clearly differentiated from other outcomes, for example, SP Sample size not powered
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	Prospective study/randomized study with no control group or very small sample size Heterogeneous sample of amputees PLP not sole outcome or unable to differentiate from other outcomes Small sample size or small number of sample with PLP
Very low quality	Any estimate of effect is very uncertain	Case study Very low number case series

Source: Data from Guyatt et al.[21]
Abbreviations: PLP, phantom limb pain; SP, stump pain.

potential risks of bias were determined to impact on the confidence in the estimate of the effect from that study, and the more the risks, the lower the GRADE classification.

Data extraction and synthesis

All papers were reviewed by the first author and any doubts resolved by discussion with the second author. Each treatment was isolated and considered individually. Due to the general low quality of the studies, it was only possible to analyze the data narratively.

Results

Various systematic reviews were identified and used to confirm the appraisals of individual treatments, except for two robust and recent reviews of mirror therapy and associated treatments. Due to the complexity and number of different mirror therapy and associated techniques that have been tested, only the systematic review results are reported.

Eighty-six papers were appraised. One study plus the two systematic reviews were assessed to be of high quality, nine were assessed as moderate quality (Table 4) and 75 as low or very low quality (Table 5). Pharmacologic, surgical and nonpharmacologic treatments have been used to treat PLP.

High-quality evidence

A systematic review of 20 mirror therapy studies and another of 15 studies of movement representation techniques (often utilized alongside mirror therapy) to control PLP have found insufficient evidence to support their use for PLP.[20,22]

One high-quality double-blind, placebo-controlled trial (n=54) using repetitive transcranial magnetic stimulation to stimulate the primary motor cortex of traumatic amputees (land mine victims) found a significant reduction in pain visual analog scale (VAS) at 15 days (p=0.03); however, there was no longer a statistical difference at 30 days.[23]

Moderate-quality evidence

One RCT[24] which used pain intensity as the primary outcome (n=39) found no difference between amitriptyline and the active placebo benztropine. Function was measured as a secondary outcome and this too showed a nonsignificant difference, while satisfaction with life was higher (p=0.04) in the placebo group. Fifteen side effects were reported, with dry mouth being the most severe in the amitriptyline group.

Two randomized, double-blind, cross-over studies comparing gabapentin with placebo[25,26] were found. Methodologically, both were well constructed; but as they used inactive placebo and had low sample sizes, 19 (complete data on 14) and 24, respectively, they were judged to be of moderate quality. Bone et al found that gabapentin statistically reduced pain intensity at 6 weeks. The average VAS reduced from 6.6 (SD 1.8) to 2.9 (SD 2.2) in the gabapentin group, as compared to a reduction from 6.7 (SD 1.9) to 5.1 (SD 2.2) in the placebo group. No statistical difference

Table 4 Details of papers assessed to be of moderate quality with reasons for potential bias identified

Reference	Methods	Participants	Outcomes	Risk of bias
Bone et al[25]	Gabapentin RCT, double-blind, cross-over, inactive placebo Population PLP >4/10 for 6 months	33 referred 19 recruited (16 males) 14 completed 15 lower limb amputees	PLP VAS difference from baseline (p=0.025 at 6 weeks point, otherwise ns) HAD (ns) Bartel index (function), ns Sleep interference (ns)	Small sample size Inactive placebo Multiple tests performed VAS 6 weeks result may be artifact
Maier et al[31]	Memantine Double-blind, placebo-controlled RCT PLP for at least 1 year (>4/10) 4 weeks follow-up	36 participants Mixed upper/lower limb Mixed major/minor amputation	PLP VAS (ns)	Mixed group Short follow-up Small sample size Unclear how PLP and SP are differentiated
Nikolajsen et al[29]	Memantine Double-blind, cross-over RCT PLP or neuropathic pain postamputation >3/10	19 participants (14 males) 4 nerve injury 7 finger amputations 1 upper limb amputation 7 lower limb amputations	Daily mean VAS (ns) MPQ (ns) Evoked pain (ns)	Mixed group of conditions/amputations Small sample size Worst pain used, so unclear effect on PLP
Nikolajsen et al[28]	Ketamine Double-blind, cross-over RCT, inactive placebo	11 participants (8 males) PLP or SP 3 finger amputations 2 upper limb 6 lower limb 7 cancer 1 trauma 3 surgical	VAS (p<0.05) MPQ (p<0.05) Evoked pain (p<0.05 for some areas only)	Mixed PLP and SP Mixed amputation/level Small sample size Short duration of effect Side effects of ketamine
Robinson et al[24]	Amitriptyline RCT, active placebo (benztropine) Amputation-related pain for at least 6 months	39 participants Mixed upper/lower limb 7 PLP, 6 SP, 24 both, 2 other pain	Average VAS (ns) MPQ (ns) BPI (ns) Function (FIM), ns Satisfaction with life (ns) Handicap (CHART), ns	Mixed amputation Mixed PLP and SP Small sample size
Smith et al[26]	Gabapentin Double-blind, cross-over RCT, inactive placebo	24 participants Lower limb amputation PLP or SP (VAS >3 in the last month)	Composite NRS (0–10), ns Global benefit score (p<0.05) BPI (ns) MPQ (ns) Depression (CES-D), ns Function (FIM), ns Satisfaction with life (ns) Handicap (CHART)	Mixed pain PLP/SP Small sample size Inactive placebo
Wiech et al[30]	Memantine Double-blind, cross-over RCT, inactive placebo	8 participants Upper limb 4 above elbow 3 shoulder 1 hand PLP only	Mean VAS during treatment (ns) MEG scan (cortical reorganization), ns	Small sample size Inactive placebo Mixed upper limb sample
Wu et al[32]	Lidocaine and morphine Double-blind, cross-over RCT, active placebo (diphenhydramine)	31 participants PLP or SP or both Upper/lower limb amputees (9/22)	Pain VAS (lidocaine SP – p<0.01) (morphine SP – p<0.01 and PLP – p<0.001) Sedation VAS pain relief score (%) NNT (lidocaine – SP 2.5 for 30% reduction) (morphine – SP 2.1 for 30% reduction and 1.9 for 30% reduction in PLP)	Mixed sample of amputees PLP and SP Small sample size for multiple calculations Short follow-up (80 minutes)
Wu et al[33]	Mexiletine and morphine Double-blind, cross-over RCT, inactive placebo	60 enrolled, 45 two drug periods, 35 all three phases	Pain VAS change from baseline Morphine pain relief vs placebo p=0.0003 and vs mexiletine p=0.0003 Morphine NNT for 33% pain reduction =4.5 Side effects high in morphine group	Mixed sample of amputees PLP and SP Large dropout Inactive placebo

Abbreviations: BPI, brief pain inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CHART, Craig Handicap Assessment and Reporting Technique; FIM, Functional Independence Measure; HAD, hospital anxiety and depression scale; MEG, Magnetoencephalography; MPQ, McGill pain questionnaire; NNT, number needed to treat; NRS, numerical rating scale; ns, no statistical difference; PLA, phantom limb awareness; PLP, phantom limb pain; PLS, phantom limb sensation; RCT, randomized controlled trial; SP, stump pain; VAS, visual analog scale.

Table 5 Low- and very low-quality studies

Treatment type	Specific treatment	Number of studies	Outcomes	Comments
Antidepressants (tricyclic)	Amitriptyline Doxepin	Two case studies One case series (n=5)	Reduction in pain intensity	Side effects Case series combined medication
Anticonvulsants	Gabapentin Pregabalin Topiramate Carbemazepam Clonazepam	One case series (n=7) Five case studies	Reduction in pain intensity	Small sample sizes
Calcitonin	Calcitonin	One review One case series (n=10) One double-blind, cross-over trial (n=10)	Reduction in pain intensity No reduction in pain intensity	Review focused mainly on acute PLP Side effects in all studies
NMDA receptor antagonists	Ketamine	One double-blind, cross-over trial (n=10) One case series (n=3) One case study One case study	Reduction in pain intensity Pain exacerbated	Side effects in all studies Dextromethorphan and methadone have mixed analgesic effect
	Memantine	One case series (n=2)	Reduction in pain intensity	
	Dextromethorphan	One case series (n=3)	Reduction in pain intensity	
	Methadone	One case series (n=4)	Reduction in pain intensity	
Local anesthetics	Lidocaine	One randomized study (n=14)	No reduction in pain intensity	Compared with botox
	Mexiletine	One case series (n=3)	In 2/3, pain intensity reduced	Small sample size
	Ropivacaine	One case series (n=8)	In 6/8, pain reduction achieved	Peripheral nerve block
	Bupivacaine	One case study	Pain intensity reduced	Contralateral myofascial injection
Opioids	Morphine Fentanyl	One case study (n=12) Three case studies	Reduction in pain intensity	Small sample sizes
Beta-blockers	Propranolol	Three case studies	Reduction in pain intensity	Dated
Serotonin reuptake inhibitors	Fluoxetine Duloxetine Milnacipran	Three case studies	Reduction in pain intensity	Small sample sizes
Surgery	DREZ	Two case series		Unable to determine PLP effect due to mixed group
		Two case series	36% and 64% achieved pain reduction, respectively	Mixed samples and small numbers with PLP
		One case study	Reduction in pain intensity	Single case
Acupuncture	Acupuncture	Three case studies	Reduction in pain intensity	Small sample sizes
	Electroacupuncture	One case series (n=9)	In 5/9, 50% reduction in pain intensity	Small sample size
Farabloc	Farabloc	One double-blind, cross-over study (n=52)	Reduction in pain intensity	Large dropout high risk of bias
Feedback	Biofeedback	Two case series (n=16; n=9) Two case studies	Reduction in pain intensity	Small sample sizes
	Sensory discrimination	One controlled comparative study (n=10)	Reduction in pain intensity	Inactive placebo Low sample size
Hypnosis	Hypnosis	Two case series (n=25; n=20)	Reduction in pain intensity	Mixed group PLP/stump pain
Reflexology	Reflexology	One case series (n=10)	Reduction in pain intensity	Small sample size
Stimulation therapies	TENS	Two trials Seven case series or case studies	Reduction in pain intensity	Dated Small sample size Small numbers
	SCS	Five case series	Reduction in pain intensity	Lack of specificity and small sample sizes
	Motor cortex stimulation	Six case series	Variable results	In largest sample (n=5), only one achieved a reduction in pain
	DBS	Two case series	Variable results	Small sample sizes
	ECT	One case series (n=2) One case study	Reduction in pain intensity	Small sample sizes
Therapeutic touch	Therapeutic touch	Two case series	Reduction in pain intensity	Total number n=6

Abbreviations: DBS, deep brain stimulation; DREZ, Dorsal-Root Entry Zone; ECT, electroconvulsive therapy; NMDA, N-methyl-D-aspartate; PLP, phantom limb pain; SCS, spinal cord stimulation; TENS, transcutaneous electrical nerve stimulation.

was found for function. Smith et al measured all four of the important IMMPACT outcomes. No statistical difference in pain intensity was found between the gabapentin group and the placebo group, but participants experienced a statistically significant difference in their pain global improvement scale. The difference from baseline VAS for worst PLP was 1.15 (SD 2.41) in the gabapentin group and 0.58 (SD 2.86) in the placebo group, but the participants considered this to be a meaningful reduction. Changes in function scores were not significantly altered and a larger percentage of participants believed that the benefits of gabapentin outweighed the side effects (54.2% vs 16.8%). A recent systematic review[27] confirmed our appraisal and identified one additional study by Nikolajsen et al which was excluded here as it used gabapentin pre-emptively and immediately postamputation.

A randomized, double-blind, cross-over study of moderate quality due to short duration of effect measurement (80 minutes), low sample size (n=11), mixed group of amputees and mixed PLP/SP found that ketamine reduced average PLP intensity to <10% of the average baseline VAS value.[28] Nine of the 11 participants experienced side effects during ketamine infusion.

Memantine has three moderate-quality (small and mixed samples using inactive placebo) randomized, double-blind, placebo-controlled studies, all of which found no statistical difference in pain VAS.[29–31]

There is one moderate-quality (mixed group of amputees with PLP or SP or both) randomized, double-blind, cross-over study which compared lidocaine with morphine and an active placebo (diphenhydramine) on 31 amputees. No statistically significant reduction in PLP intensity was found for lidocaine during and up to 30 minutes after the completion of an intravenous infusion.[32] In the same study, morphine significantly reduced pain intensity with a number needed to treat for PLP of 1.9, but as pain VAS was only measured for 30 minutes after the end of an intravenous infusion, this can only be judged as effective for this short period of time.

A follow-up moderate-quality RCT (inactive placebo, high dropout and mixed sample) comparing morphine, mexiletine (the oral derivative of lidocaine) and placebo found that morphine reduced pain by 53% (p=0.0003). No statistical difference was found for mexiletine.[33]

Low-/very low-quality evidence

Pharmacologic treatments

The following pharmacologic treatments have been tried for PLP: amitriptyline,[34,35] doxepin,[35–37] gabapentin,[38] pregabalin,[39] topiramate,[40] carbemazepam,[41,42] clonazepam,[43] calcitonin,[44–46] ketamine,[46–49] memantine,[50] dextromethorphan,[51] methadone,[52] lidocaine,[53] mexiletine,[54] ropivicaine,[55] bupivacaine,[56,57] morphine,[35,58,59] fentanyl,[60] propranolol,[61–63] fluoxetine,[64] duloxetine[39] and milnacipran.[65] The vast majority found that PLP intensity was reduced, but the low methodological quality and small sample sizes mean that no clinical decisions should be made based on these studies.

Surgical treatments

Various authors have reported that neurectomy, rhizotomy, sympathectomy, cordotomy and myelotomy have all been attempted as treatments for PLP,[66–69] but no papers were found for any of these surgical treatments. The only surgery used to treat PLP identified by this search is Dorsal-Root Entry Zone lesioning.[70–74] Lack of specificity and low sample size make it impossible to make any conclusions about the effect of Dorsal-Root Entry Zone on established PLP.

Nonpharmacologic treatments

The following nonpharmacologic treatments have been tested on PLP: acupuncture/electroacupuncture,[75–79] biofeedback and other feedback mechanisms,[80–84] Farabloc,[85] hypnosis,[86–91] reflexology,[92] transcutaneous electrical nerve stimulation,[93–101] spinal cord stimulation,[102–107] motor cortex stimulation,[107–112] deep brain stimulation,[113,114] electroconvulsive therapy,[115,116] transcranial magnetic stimulation[117–119] and therapeutic touch.[120,121] Once again, the majority found a reduction in pain VAS; however, these are small case studies or case series, hence no clinical judgments should be made based on these results.

Discussion – the challenges for future research

If mirror therapy and associated techniques are considered as a single therapy, then 38 different treatments/therapies have been reviewed. The quality of the majority of PLP treatment studies is low, with only three papers appraised to be high quality: two systematic reviews of mirror therapy and associated techniques plus one study on repetitive transcranial magnetic stimulation. All three have produced equivocal findings and do not help clinicians to decide treatment regimens; but from the nine moderate-quality papers, there is tentative support for the use of gabapentin, ketamine and morphine. This tentatively agrees with the recommendations from a recent consensus conference on neurorehabilitation which included the treatment of PLP.[122] The consensus included other treatments found to have efficacy in the other conditions that the conference discussed and, hence, has a lower specificity than our current review.

One factor that limits the ability to judge the research performed so far is that a meaningful pain reduction for PLP is not known. Smith et al's study on gabapentin is the only one that measured meaningful pain relief. In this case, the participants stated that an average VAS reduction of 1.15 cm was meaningful even when compared to the average reduction of 0.58 cm achieved by the inactive placebo. This relatively small change was not statistically significant, but was clinically significant to the participants. It is likely that all pain conditions will have different values for a meaningful level of pain reduction and it is possible that the higher the baseline VAS, the greater the reduction that has to be achieved.[123] In complex regional pain syndrome, one study found that a relative 50% or absolute 3 cm reduction is clinically meaningful.[124] Future studies need to ensure that a global impression of change in pain is utilized to allow an assessment of what practitioners need to achieve from any therapy. Unfortunately, this does not help in the decision making for the treatment of PLP because if a reduction of <1 cm on VAS is sufficient, then it becomes possible that most of the therapies utilized previously, which reduced pain intensity, should be re-evaluated in more robust trials.

Furthermore, the fluctuant nature of PLP has not been factored into studies so far. It has been identified that commonly, amputees with PLP have 1–10 episodes a day and the most common duration for an episode is 1–10 minutes.[1,5] However, these groups do not necessarily overlap; so, someone having 10 episodes a day with each episode being 1 hour in duration is experiencing pain for 10 hours a day. Conversely, someone experiencing one episode lasting for 10 hours is similarly affected. This means that potentially some amputees with PLP would prefer the primary outcome to be to reduce the number or the length of the PLP episodes rather than reduce the intensity. The challenge for researchers is to build this into the methods of future studies.

The use of mirror therapy and associated techniques (including imagery, virtual reality and immersive therapies) has expanded in recent years. Current evidence though is difficult to judge, as there does not appear to be a defined standard for what constitutes mirror therapy and various mechanisms have been proposed for the effects of mirror therapy, including reversal of cortical reorganizations, relinking the visual and motor systems, activating mirror neurons in the contralateral brain, modulation of pain pathways, the reawakening of proprioceptive memories and the reversal of a potential neglect syndrome.[125–128] Future mirror therapy research needs to be refined to assist elucidation between these potential mechanisms. Currently, comparison between studies is almost impossible; so, forthcoming studies need to control for the individual elements within mirror therapy to assess which are the most important and if they are additive. Brodie et al performed the largest trial of mirror therapies; however, there are substantial weaknesses to the study.[129] Although 80 amputees were recruited, only 15 had PLP at the time of the mirror intervention. No estimate of the ongoing effects was measured to see if the participants experienced fewer episodes or less-intense episodes after the therapy. The conclusion that mirror therapy did not affect PLP, therefore, has a high risk of bias. In addition, two newer studies were not captured by the systematic reviews utilized by our review to assess the efficacy of mirror therapy and associated techniques.[130,131] Brunelli et al reported significant reduction in PLP intensity (n=51). However, it is impossible to identify which participants had PLP and which phantom limb sensation, as both were inclusion criteria; hence, potential bias remains high. Yildirim and Kanan recruited a very small sample of 15 amputees using a quasi-experimental approach and found a significant reduction in PLP intensity. Currently, therefore, these do not influence the conclusions from the previous reviews.

Experience suggests that amputees have difficulty differentiating between PLP and SP and other phantom phenomena such as exteroceptive sensation.[1] So, doubt is attributed to studies that do not convincingly resolve between these phenomena. Future studies need to be designed appropriately in order to move knowledge forward. Methodological issues considered to be important are: heterogeneity of samples, that is, upper and lower limb amputees, major and minor amputation, acute vs chronic PLP, traumatic vs surgical amputation and cancer vs non-cancer related amputation; active placebos are required for controlled trials; and follow-up time needs to be adequate. It is essential that all studies evaluating treatment for PLP use IMMPACT outcomes. Larger and better controlled studies are required and encouraged before an informed decision can be made about all therapies used to treat PLP. At present, though, there is not enough evidence to decide what would be the most appropriate treatment for people experiencing established PLP.

Disclosure

The authors report no conflicts of interest in this work.

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