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 amputees1–4 and is known to be highly fluctuant.1,5 As PLP is associated with deafferentation and is known to be associated with cortical reorganization6 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
In 1980, Sherman identified that 43 treatments had been used to control PLP\(^1\) 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.\(^1\)\(^4\)

For a while, focus turned toward the potential to prevent rather than treat PLP by aggressively controlling preemptuation or immediate postamputation pain.\(^1\)\(^5\)–\(^1\)\(^7\) Results from these studies have been equivocal with the stronger studies favoring no effect.\(^1\)\(^8\) To add to the confusion, treatments used in these studies have been the center of attention.\(^2\)\(^0\)

The search strategy is outlined in Table 1. The search was designed to identify treatments/therapies that improve one or more of the following outcomes: pain, function, and 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 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.

### 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.\(^1\)\(^8\)

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.

#### 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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Search strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step</strong></td>
<td><strong>Action</strong></td>
</tr>
<tr>
<td>1</td>
<td>“Phantom Limb” searched as MeSH term</td>
</tr>
<tr>
<td>2</td>
<td>Titles searched for treatments</td>
</tr>
<tr>
<td>3</td>
<td>List of treatments identified</td>
</tr>
<tr>
<td>4</td>
<td>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”)</td>
</tr>
<tr>
<td>5</td>
<td>Excluded non-English papers or if full text was unavailable</td>
</tr>
<tr>
<td>6</td>
<td>Excluded all papers that were not treatment evaluations</td>
</tr>
<tr>
<td>7</td>
<td>Reference lists of papers scanned for any papers not previously identified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Example of search on MEDLINE for antidepressive agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MeSH term</strong></td>
<td><strong>Hits</strong></td>
</tr>
<tr>
<td>Phantom limb</td>
<td>1725</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>6412</td>
</tr>
<tr>
<td>Phantom limb</td>
<td>1725</td>
</tr>
<tr>
<td>Doxepin</td>
<td>758</td>
</tr>
<tr>
<td>Phantom limb</td>
<td>1725</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>2133</td>
</tr>
<tr>
<td>Phantom limb</td>
<td>1725</td>
</tr>
<tr>
<td>Antidepressive agents</td>
<td>39,073</td>
</tr>
</tbody>
</table>

Total=5

### Quality assessment

The GRADE system was utilized\(^2\)\(^1\) 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

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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 RCT24 which used pain intensity as the primary outcome (n=39) found no difference between amitriptyline and the active placebo benztpine. 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 placebo25,26 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

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

<table>
<thead>
<tr>
<th>GRADE score</th>
<th>Description</th>
<th>Agreed criteria within studies used for this comprehensive review</th>
</tr>
</thead>
</table>
| 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.
**Table 4 Details of papers assessed to be of moderate quality with reasons for potential bias identified**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Gabapentin RCT, double-blind, crossover, inactive placebo</td>
<td>33 referred, 19 recruited (16 males), 15 lower limb amputees</td>
<td>PLP VAS difference from baseline (p=0.025 at 6 weeks point, otherwise n.s) HAD (ns) Sleep interference (n.s)</td>
<td>Small sample size Inactive placebo 6 weeks result may be artifact</td>
</tr>
<tr>
<td>Maier et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Memantine Double-blind, placebo-controlled RCT PLP for at least 1 year (&gt;4/10) 4 weeks follow-up</td>
<td>36 participants Mixed upper/lower limb Mixed major/minor amputation</td>
<td>PLP VAS (n.s)</td>
<td>Mixed group Short follow-up Small sample size Unclear how PLP and SP are differentiated</td>
</tr>
<tr>
<td>Nikolajsen et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Memantine Double-blind, crossover RCT PLP or neuropathic postamputation &gt;3/10</td>
<td>19 participants (14 males) 7 finger amputations 1 upper limb amputation 7 lower limb amputations</td>
<td>Daily mean VAS (n.s) MPQ (n.s) Evoked pain (n.s)</td>
<td>Mixed group of conditions/ amputations Small sample size Worst pain used, so unclear effect on PLP</td>
</tr>
<tr>
<td>Nikolajsen et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Ketamine Double-blind, cross-over RCT, inactive placebo</td>
<td>11 participants (8 males) 3 finger amputations 2 upper limb 6 lower limb 7 cancer 1 trauma 3 surgical</td>
<td>VAS (p&lt;0.05) PLP or SP MPQ (p&lt;0.05) Evoked pain (p&lt;0.05 for some areas only)</td>
<td>Mixed PLP and SP Mixed amputation/level Small sample size Short duration of effect Side effects of ketamine</td>
</tr>
<tr>
<td>Robinson et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Amitriptyline RCT, active placebo (bentropanine) Amputation-related pain for at least 6 months</td>
<td>39 participants Mixed upper/lower limb 7 PLP, 6 SP, 24 both, 2 other pain</td>
<td>Average VAS (n.s) MPQ (n.s) Function (FIM), ns Satisfaction with life (ns) Handicap (CHART), ns</td>
<td>Mixed amputation Mixed PLP and SP Small sample size</td>
</tr>
<tr>
<td>Smith et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Gabapentin Double-blind, cross-over RCT, inactive placebo</td>
<td>24 participants Lower limb amputation PLP or SP (VAS &gt;3 in the last month)</td>
<td>Composite NRS (0–10), ns Global benefit score (p&lt;0.05) BPI (ns) MPQ (ns) Depression (CES-D), ns Function (FIM), ns Satisfaction with life (ns) Handicap (CHART)</td>
<td>Mixed pain PLP/SP Small sample size Inactive placebo</td>
</tr>
<tr>
<td>Wiech et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Memantine Double-blind, cross-over RCT, inactive placebo</td>
<td>8 participants Upper limb 4 above elbow 3 shoulder 1 hand</td>
<td>Mean VAS during treatment (n.s) MEG scan (cortical reorganization), ns</td>
<td>Small sample size Inactive placebo Mixed upper limb sample</td>
</tr>
<tr>
<td>Wu et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Lidocaine and morphine Double-blind, cross-over RCT, active placebo (diphenhydramine)</td>
<td>31 participants PLP or SP or both Upper/lower limb amputees (9/22)</td>
<td>Pain VAS (lidocaine SP – 0.01) (morphine SP – 0.01 and PLP – 0.001) Sedation VAS pain relief score (%) NNT (lidocaine – 2.5 for 30% reduction) (morphine – 2.1 for 30% reduction and 1.9 for 30% reduction in PLP)</td>
<td>Mixed sample of amputees PLP and SP Small sample size for multiple calculations Short follow-up (80 minutes)</td>
</tr>
<tr>
<td>Wu et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Mexiletine and morphine Double-blind, cross-over RCT, inactive placebo</td>
<td>60 enrolled, 45 two drug periods, 35 all three phases</td>
<td>Pain VAS change from baseline Morphine pain relief vs placebo p=0.003 and vs mexiletine p=0.0003 Morphine NNT for 33% pain reduction =4.5 Side effects high in morphine group</td>
<td>Mixed sample of amputees PLP and SP Large dropout Inactive placebo</td>
</tr>
</tbody>
</table>

**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

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

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.
A recent systematic review\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{31} 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.\textsuperscript{33}

\textbf{Low-/very low-quality evidence}

\textbf{Pharmacologic treatments}

The following pharmacologic treatments have been tried for PLP: amitriptyline,\textsuperscript{34,35} doxepin,\textsuperscript{35–37} gabapentin,\textsuperscript{38} pregabalin,\textsuperscript{39} topiramate,\textsuperscript{40} carbemazepam,\textsuperscript{41,42} clonazepam,\textsuperscript{43} calcitonin,\textsuperscript{44–46} ketamine,\textsuperscript{46–49} memantine,\textsuperscript{30} dextromethorphan,\textsuperscript{31} methadone,\textsuperscript{52} lidocaine,\textsuperscript{53} mexiletine,\textsuperscript{54} ropivacaine,\textsuperscript{55} bupivacaine,\textsuperscript{56,57} morphine,\textsuperscript{55,58–59} fentanyl,\textsuperscript{50} propranolol,\textsuperscript{61–63} fluoxetine,\textsuperscript{64} duloxetine\textsuperscript{59} and milnacipran.\textsuperscript{55} 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.

\textbf{Surgical treatments}

Various authors have reported that neurectomy, rhizotomy, sympathectomy, cordotomy and myelotomy have all been attempted as treatments for PLP\textsuperscript{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.\textsuperscript{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.

\textbf{Nonpharmacologic treatments}

The following nonpharmacologic treatments have been tested on PLP: acupuncture/electroacupuncture,\textsuperscript{73–79} biofeedback and other feedback mechanisms,\textsuperscript{80–84} Faradloc,\textsuperscript{85} hypnosis,\textsuperscript{86–91} reflexology,\textsuperscript{92} transcutaneous electrical nerve stimulation,\textsuperscript{93–101} spinal cord stimulation,\textsuperscript{102–107} motor cortex stimulation,\textsuperscript{107–112} deep brain stimulation,\textsuperscript{113,114} electroconvulsive therapy,\textsuperscript{115,116} transcranial magnetic stimulation\textsuperscript{117–119} and therapeutic touch.\textsuperscript{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.

\textbf{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.\textsuperscript{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.\(^{121}\) 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, re-linking 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.
References


