# Peripheral Interventions for Painful Stump Neuromas of the Lower Limb

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# Peripheral interventions for painful stump neuromas of the lower limb: a systematic review

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**Abstract**

Objectives: Painful stump neuromas in lower limb amputees are a significant burden on a person's quality of life due to interference with wearing prostheses and therefore the ability to walk. Treating painful stump neuromas is a challenge perhaps reflected by the lack of clinical guidelines both in the United Kingdom and internationally. Methods: A systematic review was conducted to evaluate the efficacy of all treatments tried in the management of symptomatic neuromas in the lower limb amputation stump in order to establish whether one treatment is superior. Results: Twenty-two studies were included in the final review which examined 14 different treatments both surgical and non-surgical. Results showed that no single treatment showed superiority. Discussion: The four treatments that showed most promise included targeted nerve implantation (TNI), traction neurectomy, nerve-to-nerve anastomosis and perineurial gluing. The short follow-up times and small sample sizes of the studies highlighted the need for more robust clinical studies.

Key words: stump pain, neuroma, treatment, amputation, management

**Introduction**

Post-amputation pain (PAP) is a disabling condition which can have a significant impact on a person's quality of life due to its unpleasant symptoms and its interference with the ability to wear prostheses. [1] It is a particular problem for patients with leg amputations who often require prostheses to aid walking. Stump pain, a sub-type of PAP, is caused by a number of pathologies including vascular insufficiency, bony spurs, skin damage and neuromas.

A neuroma describes the bulbous tumour of a nerve ending that occurs following traumatic transection (such as during the primary amputation), or following traction-related nerve damage. Following dissection, the nerve fibre undergoes Walllerian degeneration distally and when re-growth occurs, the axon fibres and new Schwann cells grow in a disorganised fashion, colloquially termed "sprouting".[2] This sprouting can result in a cluster of cells (the neuroma) at the distal end of the nerve stump which subsequently has the disposition to discharge spontaneously due to increased mechanical- and chemo-sensitivity.[3] It is often this ectopic electrical activity that leads to the sensation of the electric shock-like pain of which patients complain.

Treating painful stump neuromas (PSNs) is challenging. The National Institute of Health and Care Excellence (NICE) provides clinical guidelines for pharmacological and interventional management of neuropathic pain,[4] however, the guidelines are based on studies involving participants with different chronic pain syndromes and whether these studies involved patients with PSN is unclear.[5-7] Looking beyond the United Kingdom, the only guidelines from the American Pain Society is for opioid treatment in non-cancer pain and interventional management for back pain. No European guidelines for management of PSN could be identified.[8] Although there are no clinical guidelines for the management of PSN, attention has turned to recognising different pain mechanisms (peripheral, spinal and supra-spinal) involved in PAP and that each mechanism may require a different treatment modality.[1] Targeting PAP therefore with a multi-treatment approach is now being considered as the way forward and may even lead to the emergence of clinical guidelines for this condition.[1]

In the Western world, amputation of the limb is most commonly due to vascular pathology (82% of all limb amputations) with trauma being the second most common cause.[9] The incidence and prevalence of stump pain is not well documented and there is discrepancy in the figures that are available. One long-term study of patients with leg amputations reported that 64.5% of participants experienced stump pain[10] compared with 21% reported by a different cohort study.[11] Although the risk factors for the development of painful stump neuromas has not been studied in great detail, there is emerging evidence that pre-operative pain including its intensity and duration appear to have a role.[11,12] Stokvis and colleagues identified several prognostic factors for inadequate pain relief following surgical management including unemployment, smoking and ineffective diagnostic nerve blocks.[12]

We have reviewed the literature regarding treatments that target peripheral mechanisms of PSN in an aim to alleviate pain. Peripheral interventional treatments of PSN can be broadly categorised into surgical and non-surgical, with non-surgical being sub-categorised into neuroablative and non-neuroablative. The surgical treatments reviewed in this work are traction neurectomy, nerve implantation and nerve-to-nerve anastomosis. The non-surgical treatments reviewed include injection therapies, radiofrequency, cryoablation and shock-wave therapy. In this review, we ask the question, "Is there evidence to guide treatment for symptom relief in painful stump neuromas of the lower limb? If so: what is the best choice of therapy?"

## Materials and Methods

*Search Strategy*

A literature search was carried out using MEDLINE (1946-January 2016) and Embase (1974 – January 2016), and the Cochrane Library. A broad search was conducted using MeSH headings and free-text including the terms "neuroma*", "pain*" and "treatment". MeSH headings were examined for other relevant terms relating to the various techniques used in painful neuroma management and journal references were hand-searched to identify additional articles; forward searching also took place. Following screening of titles and abstracts, experimental studies and those involving exclusively

Morton's (intermetatarsal) neuroma or acoustic neuroma were excluded. Due to the scarcity of high quality data supporting the interventions, a narrative review of data from lower evidence studies has been included.

*Article Selection*

This review focuses on peripheral interventional treatment of PSN of the lower limb. . Phantom limb pain and other causes of stump pain were not part of this study because the authors felt that these topics have been discussed in other review articles [1,3]. Articles which examined pharmacotherapy, complementary therapy or pain treatments which targeted body sites other than peripheral were not included in the review. Papers that looked exclusively at upper limb neuromas and digital neuromas were also excluded. Once all the papers were identified, we considered whether a meta-analysis could be performed.

**Results**

The search returned 470 records; there were no results found in the Cochrane Library. Following the application of exclusion criteria and removal of duplicated material, 100 abstracts were screened and 65 papers excluded for being irrelevant (non-peripheral treatment, non-interventional treatment, phantom pain only). Following back and forth hand-searching of references of these 35 papers, a further seven papers were identified as being potentially relevant including one which had yet to have MeSH headings mapped to it. These 42 papers were read in full and 20 were excluded as they were deemed inappropriate (narrative reviews, digital neuromas). Twenty-two studies were included in the final review (see tables 1,2,3) with an equal number of papers focusing on operative (11) and non-operative (11) management. Looking at the quality of evidence in the literature found, there were 14 case series/reports, six cohort studies (all without control groups), and two randomised control trials (RCTs). Fourteen different peripheral interventional techniques have been researched including seven different surgical techniques.

The most prevalent pain measurement tool was the Visual Analogue Scale (VAS) with 13/22 studies using this rating scale. Other papers used different pain measurement tools including 3 and 4-point scales, the McGill pain questionnaire and the Pain Rating Scale (PRS). Pain scales such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and painDETECT which identify

neuropathic pain from nociceptive pain were not used in any study in this review.

The average follow-up period where final assessment took place ranged between 3 and 82 months (median = 12, mode = 6, mean = 18.9 months). Sehirlioglu and colleagues[19] demonstrated that neuromas take on average 12 months to form however, only 13/22 studies had an average follow-up time of more than 12 months. All papers that evaluated surgical techniques diagnosed neuroma on the basis of clinical symptoms and none used radiological imaging either pre-operatively or during follow-up. Eight papers looked at whether patients had more comfort in wearing their prosthesis after treatment but this was only descriptive and did not use any quantitative form of measurement. Only three papers considered quality of life and again, these results were only descriptive. With regards to meta-analysis, the heterogeneity of the studies was too great to be able to pool the data and make a conclusion about the treatment effect.

**Diagnosing painful neuroma**

All studies in this review diagnosed the presence of a painful neuroma based on the patient's subjective history of localised tenderness including reproducible pain on palpation in the form of Tinel's sign. In addition to this, the finding of a sensitive, palpable lump in the proximity of a nerve or scar tissue was deemed to be a positive indicator of a painful neuroma. Twelve studies used a diagnostic block with lidocaine as a positive diagnosis. Seven non-surgical papers involved ultrasound to aid diagnosis and treatment, but only one paper used ultrasound in the follow-up.[13] For the studies examining surgical techniques, only two[18,23] mentioned sending neuromas for histological examination and only one of those two studies confirmed that specimens were true traumatic neuromas.[23] The remaining surgical papers relied on the “operative identification” of neuroma.

*Use of radiological imaging*

Seven papers used ultrasound to aid diagnosis of a painful neuroma and one paper used sonography as part of follow-up. There have been no studies analysing the sensitivity and specificity of ultrasound in the diagnosis of traumatic neuromas , nor in its usefulness in follow-up, however a meta-analysis examining diagnostic accuracy of ultrasound in Morton's neuroma demonstrated that it was superior to magnetic resonance imaging.[47]

**Surgical therapies**

Surgical therapies constitute the majority of published papers on treatments for PSN. A number of techniques have been researched including traction neurectomy, vein implantation, burial techniques (either into bone or muscle), perineurial adhesis and nerve-to-nerve anastomosis.

*Traction neurectomy*

Only two case series have been published on the outcomes of a surgical method that is most commonly used in clinical practice when treating symptomatic stump.[15,19] Traction neurectomy is the technique of gently pulling on the affected nerve before dissecting it proximally and allowing the tension to retract the severed nerve back up into soft tissue with the hope that the absence of pressure on the distal end of the nerve will be sufficient to prevent neuroma formation. The authors' experience is that the method of nerve cutting can vary according to clinician's choice. Diathermy, ligation and cutting with a blade have all been used. Sehirlioglu and colleagues (Table 1) reviewed 75 patients who had developed painful neuromas following lower limb amputation due to landmine explosions. All patients underwent traction neurectomy (unknown method of transection) and remained pain free at follow-up at mean 2.8 (range 0.5 – 6.0) years. These results differ from those reported by Pet et al. (Table 1) who reviewed 38 lower limb amputees available to follow-up after treatment, although the exact method of dissection of the nerve is not reported. Pet and colleagues found that only 58% were pain free at follow-up which was on average at 37 months (11-91 months). This study found that gender was a significant prognostic factor for treatment outcome with males being more likely to have treatment failure. However, a large prospective follow-up study by Stokvis et al.[12] showed no significant correlation between gender and treatment outcome. Pet et al. provide a thorough discussion of the limitations of their study; the largest limitations being the level of evidence of the study design, high numbers lost to follow-up and confounding factors such as concomitant bony spurs making interpretation of results difficult. Additionally, the outcome variables were somewhat limited with patients being categorised as either 'pain free' or having 'pain recurrence/persistence'. The lack of using a pain measurement tool such as the VAS means it is hard to compare with other studies.

*Vein implantation*

Following on from experimental studies which have suggested that implanting transected nerves into veins can produce more organised re-growth and reduce neuroma formation compared to controls, Koch and colleagues (Table 1) carried out two retrospective case series (n= 23 and n=8)[20,22]. All patients were experiencing moderate or severe pain based on a 4-point scale of their painful neuromas of superficial nerves before they underwent excision of the neuroma followed by implantation into a superficial vein. There were two techniques involved: implantation via venectomy (end-to-side) or where the vein was transected, with the nerve inserted and sutured into it (end-to-end). Eleven out of 23 and four out of eight patients were pain free at follow-up, the mean being 26.5 and 17.0 months respectively. Pet and colleagues demonstrated that neuroma excision alone with traction neurectomy provides slightly better outcomes within the same time frame so it is difficult to assess whether it is the vein implantation or the actual excision of the neuroma that is the determining factor in this respect.[15] This method of vein implantation is only feasible with superficial nerves and veins as using larger, deeper veins would increase the risk of thrombosis.

*Muscle implantation*

Ducic and colleagues[18] (Table 1) performed a retrospective cohort with no control group on a number of upper and lower limb amputees which investigated the outcome of nerve implantation into muscle as previously described by Dellon and colleagues.[35] This appears to be the first cohort study using this technique that involves lower limb amputation stumps. Twenty-one amputees, including three patients with above knee amputation (AKA) and 12 patients with below knee amputation (BKA) underwent this surgical procedure. In order to eliminate concomitant pathologies that could interfere with data interpretation, patients with other causes of stump pain were excluded. The mean VAS was significantly reduced from 8.04 to 1.07 post-operatively with 11/21 (52%) being pain free at follow-up which was at mean (range) 22.8 months (9-39 months). However, as with all studies that measure pain, there is likely to have been a degree of response bias.

*Comparing muscle and vein implantation*

Vein implantation was compared with muscle burial by Balcin and colleagues (Table 1) who conducted a randomised double-blinded trial (each group n=10) to look at which surgical method provided greater pain improvement.[17] Twenty patients with traumatic painful neuromas of the lower

limb (but not amputees) were allocated to undergo neuroma excision followed by one of the two treatments; all patients completed the follow-up period of 12 months. Pain improvement was measured using two tools: the McGill questionnaire and the VAS. In comparing pre-and post-operative outcomes, only the nerve-into-vein cohort achieved significance in reducing VAS scores ($p<0.01$). Comparing the outcomes of the two procedures at final follow-up, the nerve-into-vein group demonstrated improvement in pain in one pain measurement tool (McGill, $p<0.05$). The patients included were those whose neuromas developed in cutaneous nerves following orthopaedic surgery (unspecified, not amputations). The exclusion criteria were strict so that patients with previous operative neuroma management, diabetes, autoimmune disease, cancer and peripheral arterial disease were not considered; however, the two groups were comparable in baseline characteristics. Despite all patients completing follow-up, it could be argued that this was not a long enough period as one study has shown that the average length of time for neuroma formation to occur is around 12 months.[19] Although this study demonstrated that neuroma excision followed by vein implantation reduces pain, we also know that traction neurectomy has the potential to reduce pain.[15] Studies comparing traction neurectomy and vein transplantation would therefore be useful in determining which provides the better outcome for the longest amount of time. Finally, despite being a randomised trial, this was still a small study which did not include stump neuromas and therefore it is not possible to generalise the results.

*Muscle burial vs bone burial*

Chiodo and colleagues (Table 1) explored whether there was a significant difference in pain reduction when comparing burial of the proximal nerve stump into bone and into muscle.[21] Having excluded patients with complex regional pain syndrome, 27 patients with superficial peroneal neuromas were analysed in a cohort which examined their pain relief using VAS, percentage of pain relief and a 5-point pain relief scale. Patients were divided into two groups to receive the two treatments. Four patients who had ineffective pain relief with muscle burial were then put into the second group. Appropriate analysis of results demonstrated that there was a significant difference in VAS and perceived pain relief with burial into bone providing more pain relief compared to burial into muscle. However, these results are confounded by the swapping of patients from one group to another, by

concomitant orthopaedic procedures and by a dramatically shorter average follow-up for the bone implantation group. This study also involved non-stump neuromas so once again, the results cannot be generalised.

*Nerve anastomosis*

Originally described by Samii and colleagues in 1981[36] nerve-to-nerve anastomosis has been given a number of names including "centro-central anastomosis" and "centro-central short circuiting" (CCSC). The technique, which involves separating the individual fascicles of a nerve stump and anastomosing the ends together in an attempt to prevent neuroma growth, has previously been researched for its use for treating Morton's and digital neuromas. Only two low evidence papers have examined the effectiveness of the technique in treating painful amputation stump neuromas. In 1993, Barbera and colleagues wrote a case series on 22 patients with lower limb amputations secondary to peripheral vascular disease who were followed-up on average at 15 months (12-24).[23] Pain sensation (no measurement tool mentioned) before and after the procedure and the ability to wear a prosthesis was documented. Twenty-one out of 22 patients reported to be free of neuroma-type pain at follow-up with 18 being able to wear their prosthesis full-time; one patient developed another symptomatic neuroma within 4 months. Although this is very weak evidence, the follow-up time was arguably long enough to allow formation of a recurrent neuroma and the results are encouraging. However, compared to traction neurectomy, this procedure appears to be more complex, requiring the use of a particular skill set and the ability to perform microsurgery, thus making the operation more complex and time-consuming. Bouroumand and colleagues has looked at the same procedure in a more recent small cohort of eight patients who were followed up over a longer period of time of 6.8 years (1.5-12 years)[14]. VAS scores "at worst" were used for statistical analysis using Wilcoxon matched-paired test but due to the small sample and nonlinear distribution, the significance achieved cannot be interpreted. Despite this, results did show a reduction in the VAS from 7.75 ± 1.28 to 2.25 ± 1.07. Limitations of this study included the lack of a control group and the confounding factor that the anastomosis was then buried into muscle. It is therefore difficult to assess the impact of this intervention on prevention of neuroma-pain with that of CCSC.

In a more complex procedure, Pet and colleagues looked at a technique called 'targeted muscle implantation' (TNI) in a retrospective case series of 35 patients.[16] This procedure involved joining the nerve stump to a motor nerve which has been denervated from its source; this method is based on the theory that proximal nerve axons will arborise along the motor nerve branches rather than form a neuroma. In this case series, Pet et al. divided the cohort into two groups: those that had TNI as a primary procedure at time of amputation (no neuroma) and those that had TNI as a secondary procedure to treat an already established symptomatic neuroma. For those that had TNI as a primary procedure, 11/12 (92%) were free from neuroma pain at follow-up (22 months, range 8-60). For those who had secondary TNI, 20/23 (87%) were free of neuroma pain at follow up (22 months, range 4-72 months). The authors discuss the limitations of the study in good detail including the issue of transfer bias with 24% of eligible patients being lost to follow-up and issues with concomitant pathologies that could have caused the stump pain rather than the neuroma; on the other hand Pet et al. did not exclude patients with bony spurs, and treated neuroma pain as an all-or-none phenomenon which does not reflect the complexity of neuropathic pain.

*Perineurial adhesis*

This single case series by Martini and colleagues followed on from an experimental study which demonstrated that gluing the perineurium over surgically shortened fascicles prevented axon sprouting compared with ligation and capping.[24] Thirty-six patients with amputation stump neuromas (including digital neuromas) underwent the procedure described above. At follow-up, mean (range) 17 months (4-43), 28/36 were pain free. Despite these results, no further clinical studies have since looked at this technique nor do any narrative reviews give explanation as to why this technique has not been further explored. [2,37,38]

**Non-surgical methods: neuroablative therapies**

*Phenol injections*

Although phenol and other sclerosing injections have been used in the management of chronic pain in general, only one paper has followed-up the effects of ultra-sound guided phenol injections in the specific management of painful amputation stump neuroma.[27] Eighty-two amputees (71 lower limb) received either 1, 2, or 3 phenol injections into their stump neuromas. Participants rated the quantity of

their pain (VAS) and character of the pain after each treatment and finally at 6 months. Although three injections were planned for each participant, there was a high drop-out rate at each stage. The authors analysed this confounding factor and found no negative reasons for this other than the fact that the initial treatment had provided adequate pain relief; each group was homogeneous in baseline characteristics. Statistical analysis was therefore applied to three groups according to the number of injections received. Fifty-two patients were available at the 6-month follow-up. The overall median VAS score was reduced from 10 ±1.5 to 3 ±2.6 with significance achieved for each individual group. Although no participants were left entirely pain free, 20/52 (39%) reported being almost pain-free and no patients experienced worse pain compared to before treatment. Interpretation of the results was complicated by the poor participant compliance and the largest issue with the study was relating to side-effects. Ten percent of patients, 8/52, (reported as 5.1% based on total number of injections) experienced minor complications such as painful oedema, local infection and painful myopathy and two patients had major complications including soft-tissue necrosis.

*Alcohol injections*

Only one small case series of two patients was identified which examined the use of sclerosing alcohol injections in the management of PSN.[26] The first patient (BKA) with a VAS score of 10/10 due to a common peroneal nerve neuroma. Following the first injection, he remained pain free for 3 months before the pain subsequently returned to 7/10. A second injection reduced his pain to 3/10 but he was not followed-up beyond 3 months to see if the pain recurred. The second patient (AKA) with a painful sciatic neuroma (VAS 8.5). His reduction in pain was slightly less pronounced but still decreased to 4/10 for 3-months until it returned to 7/10 where he was given a second injection to good effect. Again, the lack of follow-up meant that cumulative effects of alcohol injections are unknown. Although this is only a case series of two, it seems as though the effects of alcohol injections are very short lived.

*Cryoablation*

Experimental models have demonstrated that following Wallerian degeneration post cryoablation, axon re-growth is more organised thus reducing the chance of neuroma formation. The theory is that preservation of the perineurium and epineurium which is not destroyed during cryotherapy helps this

process due to neuroplastic remodelling.[39] However, this theory is yet to be proven. Following on from studies that have demonstrated that Cryoprobe therapy has successful in treating a variety of neuropathic pain syndromes,[40,41] Caporusso and colleagues examined the clinical efficacy of cryoablation in treating painful neuromas in a prospective cohort study (n = 20).[29] Although the study reported significance in their success rate with 12 patients being pain free at one year, the majority of the neuromas studied were in fact intermetatarsal (Morton's) neuromas. There were 3 non-intermetatarsal neuromas (all cutaneous nerves of the lower limb) but the results for these neuromas were not separated from the rest. Additionally, none of the patients were amputees. Reporting a similar success rate to that of simple surgical excision, the authors stated that a randomised trial comparing the two techniques was in progress although this has not been published to date. Only one pilot study (n=10) has looked at cryoprobe therapy for the treatment of PSNs in amputees which was reported in a letter.[28] Although 9/10 patients reported pain improvement at 3 months, only 3 patients were still experiencing pain relief 1 year following the procedure whilst 8/10 reverted back to pre-treatment pain levels and 1 patient reported pain worse than before.

**Non-surgical methods: non-neuroablative therapies**

*Steroid injections*

The literature search only identified one cohort study describing the use of steroid injections in PSN. In 14 patients diagnosed with PSN using the patient's history, reproducible pain, a palpable mass and ultrasound, Kesikburun and colleagues administered a single sonographically guided steroid injection into the neuroma.[30] Mean VAS scores reduced from 7.6 to 3.5 at 6 month follow-up, although three patients underwent surgical management in this time and were considered to have failed treatment. The authors acknowledged the serious limitations of this study including the lack of comparison group and short follow-up time. However, by grouping the patients into those who had greater than or less than 50% reduction in pain, they suggested a prognostic factor: those who had experienced symptoms for longer were less likely to get as much benefit from the treatment. [30]

*Extracorporeal shock-wave therapy*

Extracorporeal shock-wave therapy (ESWT) has been used to treat pain in a number of musculoskeletal conditions including epicondylitis and calcific tendonitis of the shoulder. However,

the literature reporting results of this technique have low quality evidence and the results have been variable.[42] The physiological effects of ESWT are still theoretical but researchers believe that pulsations can cause tissue breakdown and scar re-modelling; this can allow any tension that may be on a neuroma to be released thus reducing ectopic activity and pain. Only one paper was found in the literature search which explored ESWT in treating PSNs in a controlled trial.[13] Following serial enrolment of thirty amputees (digital, upper limb and lower limb), Jung and colleagues randomised (details of randomisation not specified) the participants to receive either a ESWT once a week for 3 weeks or transcutaneous electrical nerve stimulation (TENS) with pharmacotherapy (details not specified). Pain before and after treatment was measured using a number of tools including the VAS, McGill pain questionnaire and pain rating scale (PRS); neuroma size was also measured. Final assessment at three months revealed that both treatments showed a significant difference in pain reduction across all pain scales. The EWST group, however, achieved greater mean pain reduction most apparent using the PRS. No patients were pain free at the end of the study but there were no complications and no patients experienced worse pain. The study also revealed no significant change in the neuroma size. Although this study suggests that ESWT performs better than conventional TENS and pharmacotherapy, there were several limitations, namely the short follow-up time, small sample size and the variation in the number of different amputation levels. There was also no mention of ethical approval. It would have useful to have a few more details such as the length of time between amputation and neuroma symptoms and how the authors accounted for other factors such a simultaneous PAP unrelated to the neuroma. It may also be useful to compare EWST against a number of other treatments used for treating PSN.

**Radiofrequency treatments**

Another technique that is increasingly being researched in the treatment of a variety of chronic pain conditions is radiofrequency (RF).[43] There are two broad classes of RF: ablative thermal lesioning and pulsed RF which is generally conducted at lower temperatures and is not associated with gross tissue destruction. RF thermal lesioning tends to be practices in two forms: short bursts of relatively high energy as in surgical diathermy and the more prolonged, controlled application of relatively low-energy RF. Four low evidence papers reporting the effects of peripherally administered pulsed

radiofrequency on patients with PSN were identified (Table 4). West and colleagues described a case series of four patients (three post-AKA and one above elbow amputee) who were experiencing significant stump neuroma pain and were completely unable to wear their prosthesis.[33] Following treatment with pulsed radiofrequency delivered to the neuroma percutaneously, all 4 patients experienced complete pain relief lasting between 4-6 months and were able to tolerate the wearing of their prosthesis. Two patients' pain returned by 6 months however it was less severe than before treatment. The same benefit was observed in case reports by Wilkes and colleagues,[34] Restrepo-Garces and colleagues[32] and Kim and colleagues[31] but similarly, their follow-up only lasted 6 months. Although these case reports report benefit with pulsed radiofrequency, their low quality study design and short follow-up mean that further research is needed before we can determine whether pulsed radiofrequency really is an effective treatment in the management of PSN.

*Coblation*

Coblation (cold ablation) describes a form of RF lesioning used in ENT surgery which involves applying radiofrequency through a conductive solution; this creates radical species whose energy has the ability to cause tissue breakdown without causing thermal damage. Zeng and colleagues believe that technique may have a role in treating PSN and have reported one case of a patient with AKA with a painful femoral nerve neuroma who reported a decrease of his pain by 80% which lasted 6 months until the follow-up period ended.[25] Considering this is the first reported case of using coblation in PSN, not much can be inferred from this observation but it contributes to the continuing myriad of treatments investigated for this complex condition.

**Complications**

Out of all the 11 surgical papers, three reported that no complications occurred.[14,18,24] (Table 1), six papers reported complications of infection, wound dehiscence and recurring pain.[15,17,19,20,21,23]; in two papers, there was no mention as to whether there were any complications. There was no mention of any complications in three of the non-surgical papers [30,31,34], six reported that there were no complications[13-,25,26,29,32,33],and two papers reported complications [27,28] which included infection and tissue necrosis with phenol injections and worse pain with cryoablation (Tables 2-4).

**Discussion**

*Statement of findings*

Although some treatments have shown promise, this review demonstrates that there is a lack of evidence to quide the peripheral management of lower limb PSNs. Within this review, Targeted Nerve Implantation demonstrated the most impressive results. Although very low level evidence, traction neurectomy also provided good results. The remaining two techniques that have shown promise are nerve-to-nerve anastomosis and perineurial gluing.That so many different treatments have been explored for the management of painful neuromas demonstrates that not one single treatment modality is superior. However, this conclusion is based on a review of studies that either have a small sample size or a short follow-up time. We therefore call for more research, both surgical and non-surgical, with greater numbers of participants and longer follow-up times.

*Discussion of findings*

Stump neuromas are common sequelae of limb amputation but not all neuromas are painful. When a stump neuroma does become symptomatic, it is a significant cause of morbidity and therefore finding a treatment that is effective for a long period of time with few side-effects is the main goal of treatment. Hsu and colleagues described the pathophysiological basis of post-amputation pain as involving peripheral, spinal and supra-spinal mechanisms and highlighted the importance of therapy being individually tailored and mechanism-based.[1] Stump pain, whether due to neuroma or a bony spur, is predominantly recognised as being a peripheral mechanism and therefore it can be argued that treatments should primarily be peripherally focused. Despite this, the current evidence for peripherally-based treatments is poor. Furthermore, before a superior peripheral interventional treatment has been established, new research into treating spinal mechanisms in the management of PSN is taking place.[46]

Studies looking at the effectiveness of treatments for PSNs are extremely difficult to execute due to the subjective nature of pain and other qualitative-based outcomes such as quality of life and ability to perform activities of daily living (ADLs) . Neuroma pain is extremely variable in terms of intensity, frequency and duration; it is often worse when the patient is using a prosthesis. Patients can fjnd it hard to differentiate between the sub-types of stump pain and between nociceptive and neuropathic

pain. Differentiation between nociceptive and neuropathic pain is possible through using tools such as painDETECT and LANSS. Other pain assessment toolsassess the effects of pain on activities of daily living (McGill),the nature (character) of the pain as well as the intensity, and those that simplify pain into a 10-point scale (VAS). A phenomenon as complex as PAP requires complex measurement tools however, this becomes very challenging when interpreting the results and comparing studies. It is important that future studies try and standardise the use of pain measurement tools.

*Strengths and limitations of this critical appraisal*

Despite there being a number of narrative reviews on the subject of neuroma pain and is management [1,2,37,38,45,46] we believe that ours is the first attempt at a systematic review., albeit with a number of limitations. It is difficult to know whether all potential papers for review have been identified; publication bias will certainly have played a role. For example, there was one publication that was not found in the literature search despite it involving PSN management as the MeSH heading included "phantom pain" and "stump pain" was only mentioned in the body of the text.

The original research question was primarily concerned with lower limb stump neuromas because there are different considerations with regards to achieving good pain relief compared with non-stump neuromas and upper limb neuromas. As the lower limb is involved with weight-bearing, most amputees of this body part require the use of a prosthesis in order to ambulate. Due to the mechanically sensitive nature of neuromas, wearing a prosthesis is often problematic, arguably more so than the upper limb amputee with a symptomatic neuroma. Given this consideration, there was some uncertainty as to whether to include research papers that involved a mixture of upper limb and lower limb stump neuromas as well as papers that involved both amputation neuromas and non-amputation neuromas. It was decided that papers looking exclusively at digital and upper limb stump neuromas would be excluded. This decision was based on a number of reasons. Firstly, the volume of literature that looks at exclusively at upper limb neuromas is vast and would detract away from the original research question; subsequently the authors believe that digital neuromas warrant special consideration due to the complex nature, function and size of hand anatomy. Similarly, the review was limited in such that it only focused on one type of amputation pain. It was felt that broadening the scope to include management of phantom pain or other causes of stump pain would make the paper

too long. The decision to focus on a fairly narrow topic was because other literature has explored post-amputation pain as an entire phenomenon.[1]

Another limitation of this review relates to the level of evidence of the literature. The ideal studies to answer the research question would have been RCTs and cohort studies with control groups, however, the level of evidence of literature in this review was weak and therefore any conclusions will be tenuous. In order to write a good quality systematic review, there needs to be a sufficient number of studies of sound methodology looking at the same treatment method. Low level evidence papers could have been excluded but this would have left eight papers with no more than two studies looking at the same treatment. In addition to the variety of study designs, the actual number of treatments being researched as well as their different outcomes being measured makes meta-analysis extremely difficult and the results of this study had to be presented in a non-statistical format.

*Other potentially important outcomes*

The authors appreciate that looking exclusively at pain scores is simplistic and not reflective of the complexity of this clinical condition. Other outcomes that were not analysed but are important to consider when evaluating the benefit of painful stump neuroma treatment include quality of life, the ability to perform ADLs, and the ability to wear a prosthesis. It was felt that the studies in this review did not measure these other outcomes in enough detail to be able to draw any meaningful conclusions.

*Recommendations for practice*

We suggest the use of radiological imaging as part of the clinical work-up in diagnosing the cause of stump pain: ultrasound to idenitify any neuroma and xrays to identify bony spurs. This allows concomitant pathology to be identified and treated adequately. We also recommend follow-up ultrasound at three and 12 months in patients who have undergone excision and have recurrence of symptoms to objectively demonstrate whether the neuroma has recurred. Pet and colleagues observed that stump neuromas are most frequently managed by traction neurectomy in clinical practice and the authors of this review note the same.[15] In the knowledge that there are many patients regularly undergoing revision surgery, it is unknown why more robust clinical trials have not taken place. The need for better documentation on the incidence and prevalence of PSNs as well as more research into these treatment methods is long overdue.

The authors of this study suggests that any clinical study in this domain which takes place from now on should have a minimum follow-up period of 12 months with follow-up being performed at the same time-points. There should be explicit detail of how the procedure was performed and how the pain was measured with standardisation of pain scales and above mentioned outcomes; finally a comparison group would be of benefit in determining the effect of the treatment.

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| Table 1: Surgical therapies | | | | | | |
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| Author (Date) | Intervention | Outcomes | Study Design | Size | Results | Comments |
| Bourouman d (2015)[14] | Nerve-to-nerve anastomosis – "Centro-central short circuit" | qVAS score before and after interventio n<br>Ability to wear prosthesis<br>Quality of life<br>Medication | Retrospectiv e cohort (no comparison group) | 8 (6 AKA, 2 BKA) | Mean qVAS pre-op: 7.75± 1.28<br>At follow-up (mean 6.8 years): 2.25 ± 1.07 | No comparison group<br>Mann-Whitney U test used for significance in addition to Wilcoxon signed rank test<br>Small sample size<br>Confounding factor – nerve stump also buried into muscle<br>No mention as to whether participants had other types of post-amputation pain<br>QoL measured as an additional outcome<br>No reported post-operative complications |
| Pet (2015)[15] | Traction Neurectomy | Pain (yes or no) following | Retrospectiv e case series | 38 (30 BKA, 8 AKA) | 22/38 (58%) pain free at | Follow-up bias<br>Confounding factors such as concomitant |

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| | | traction neurectomy ? Secondary outcome: reoperation , recurrent symptomatic neuroma | | | follow-up (mean 37 months) | pathologies that could cause stump pain not reported Patients with phantom limb pain not recorded Did not measure ability to wear prosthesis or QoL as an outcome Radiographic imaging not used for diagnosis or follow-up Other than treatment failure, no other complications were mentioned |
| Pet (2014) [16] | Targeted Nerve Implantation | Presence or absence of neuroma pain | Retrospective Case series | 35 (23 lower limb amputations) | Secondary TNI, 20/23 (87%) were free of neuroma pain at follow up (22 months, | Included patients with phantom pain Minimum follow-up time too short 24% lost to follow-up No radiological imaging to aid diagnosis of neuroma |

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| | | | | | range 4-72 months). | Outcomes excluded QoL<br>No mention as to whether there were any post-operative complications<br>Radiological imaging not used as objective measurement/diagnosis or follow-up |
| Balcin (2009)[17] | Muscle vs vein implantation | VAS<br>McGill<br>Trigger mechanisms<br>Social parameters<br>Patient satisfaction | RCT | 20<br>Traumatic lower limb neuromas but not stump neuromas | At 12 months:<br>VAS scores:<br>vein group 7.4±1.3 to 3.8±2.4<br>muscle group 8.1±1.4 to 5.8±2.7<br><br>McGill score:<br>vein group 32±12 to 14±12 | Small sample size<br>Not amputation stump neuromas<br>Presence of other concomitant pain not recorded<br>Radiological imaging not used in diagnosis or neuroma or follow-up<br>2 patients developed post-operative wound infection in the muscle group<br>Use of more in-depth pain tool (McGill) including |

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| | | | | | muscle group 39±13 to 33±18 | characteristic description of pain |
| Ducic (2008)[18] | Neurectomy and muscle implantation | VAS scale<br>QoL<br>Ambulation status<br>Absence of spasms | Retrospective cohort with no comparison group | 21 (15 AKA/BKA)<br>Remainder UL amputations | Mean VAS score reduced from 8.04 ± 1.18 to 1.07±1.59 ($p<0.0001$) at follow-up (mean 22.8 months) | Assessor and participant bias<br>Lack of control group<br>Analysed a number of outcomes including QoL, ability ot wear prosthesis<br>Radiological imaging not used in diagnosis or as outcome variable<br>No intraoperative or post-operative complications reported |
| Sehirlioglu (2007)[19] | Traction Neurectomy | Use of prosthesis<br>Absence or presence of | Retrospective Case series | 75 (52 BKA, 23 AKA) | All pain free at follow-up mean 2.8 years (6m-6y) | No mention of pain measurement tools<br>No detail of surgical methodology<br>Low quality study design |

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| | | pain at follow-up | | | Pain tool not specified | QoL not analysed<br>Wound dehiscence reported in 3 patients which was resolved with revision surgery |
| Koch (2004)[20] | Nerve stump transplantation into a vein | Pain (Herndon 4-point scale)<br>Interference with daily activities (5-point scale) | Retrospective case series | 8 (4 lower limb amputees; level of amputation not specified) | 4/8 pain free (grade 1) and 3/8 mild pain at follow-up (mean 17 months), | Mixture of amputees and non-amputees<br>Small study<br>Did not look at QoL<br>No radiological imaging used for diagnosis or follow-up<br>No complications reported other than recurrence of minor pain at follow-up |
| Chiodo (2004)[21] | Bone vs muscle implantation for superficial peroneal neuromas | 10-point verbal pain analog scale<br>Perceived "percentage relief" scale (0-100%) | Cohort (no control) | Group A: 16<br>Group B: 11 | VAS score and perceived % of pain relief significantly better for burial into | Participants swapped between groups<br>Concomitant orthopaedic procedures took place<br>Small sample size<br>no lower limb |

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| | | | | | bone compared to muscle group | amputees<br>No radiological imaging used for diagnosis or follow-up<br>4 patients in group A required revision surgery due to recurrent neuropathic pain. 5 patients in group A developed temporary deafferentation pain. Similar complications reported in group B |
| Koch (2003)[22] | Vein implantation | Pain (Herndon 4-point scale)<br>Interference with daily activities (5-point scale) | Retrospective case series | 23 (7 unspecified amputations) | 12/23 completely pain free (grade 1) at follow-up (ave. 26.5 months) | Variety of different mechanisms for neuroma. No details as to type of amputation.<br>Small sample size<br>Low quality study design<br>Used a simple grading system to |

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| | | | | | | measure disability in addition to pain<br>No radiological imaging used for diagnosis or follow-up<br>No mention of any complications |
| Barbera (1993)[23] | Nerve-to-nerve anastomosis | Absence of neuroma pain at follow-up<br>Ability to wear prosthesis | Case series | 22 (20 AKA, 2 BKA) | 21/22 patients had complete relief at follow-up (average 15months) | Moderate follow-up time (mean 15 months)<br>Pain measurement tool not used<br>Phantom limb pain not present in any participants<br>No radiological imaging used for diagnosis or follow-up<br>One patient had deep local infection post-operatively.<br>The same patient had neuroma recurrence at the site of the anastamosis. |

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| Martini (1989)[24] | Perineurial gluing | Absence of pain at follow-up | Case Series | 36 (all had stump pain) | 33/36 were improved or pain free at follow-up (average 17 months) | Low quality evidence<br>Small sample size<br>No pain tool used<br>No other outcomes measured<br>No post-operative complications |

CCSC, "Centro-central short circuit", the procedure that describes anastomosing nerve ends to one another; AKA, above knee amputation; BKA, below knee amputation; VAS, visual analogue scale; VAS-A, visual analogue score when active; PRF, pulsed radiofrequency; TNI, targeted nerve implantation; ESWT, extra-corporeal shock wave therapy; RCT, randomised control; QoL, quality of life; US, ultrasound; PLP, phantom limb pain

**Table 2: Neuroablative Therapies**

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| Lim (2012)[26] | Alcohol injections | Difference in mean VAS score | Case series | 2 AKA | Some benefit. Pain recurred to some degree after 1st injection<br>VAS scores<br>Case 1: 10 to 3<br>Case 2: 8.5 to | Short follow-up time (3m)<br>Anecdotal, small sample size<br>QoL or ability to use prosthesis not assessed<br>Use of ultrasound to visualise neuroma |

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| | | | | | 4 | but not used in follow-up<br>No complications reported |
| Gruber (2008)[27] | Phenol injections | Pain quantity (VAS, 3-point scale) and pain quality (character) | Prospective cohort | 82 (71 lower limb, no further details) | VAS score:<br>All patients 10±1.5 to 3±2.6 at 6 months (ave follow-up)<br><br>7/52 (13%) pain free at 6m<br>13/52 almost pain free<br>10% minor complications | Radiological imaging (ultrasound) used as part of diagnosis<br>No comparison group<br>Poor participant compliance making some groups very small size<br>Assessor bias<br>5.8% minor complication rate (painful oedema, painful local myopathy, local infection)<br>Major complications reported in 1.3% of participants included local soft-tissue necrosis and infectious erysipeloid |

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| Neumann (2008)[28] | Cryoablation | 3-step pain scale | Case series | 10 (9 lower limb amputations) | At 12 months, 3 patients had pain better to before treatment, but 7 patients had recurring pain. (3-step pain scale; equal, better or worse) | Anecdotal evidence<br>No other outcomes mentioned<br>One patient reported pain being worse after treatment |
| Caporusso (2002)[29] | Cryoablation | VAS score | Cohort, no control | 20 (lower extremity neuroma, no further details) | Initially all pain free then patients divided into 3 groups with regards to pain at 12 months:<br>Pain-free (n=12)<br>Return to partial pain (n=14) | Lack of comparison group<br>No details as to whether the neuromas were in amputation stumps<br>No other outcomes measured<br>No side effects reported |

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| | | | | | Return to full pain (n=5) | |

CCSC, "Centro-central short circuit", the procedure that describes anastomosing nerve ends to one another; AKA, above knee amputation; BKA, below knee amputation; VAS, visual analogue scale; VAS-A, visual analogue score when active; PRF, pulsed radiofrequency; TNI, targeted nerve implantation; ESWT, extra-corporeal shock wave therapy; RCT, randomised control; QoL, quality of life; US, ultrasound; PLP, phantom limb pain

**Table 3: Other Therapies**

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| Kesikburun (2014)[30] | Steroid Injections | 11-point pain scale | Cohort with no control | 14 (12 BKA, 2 AKA) | Mean VAS score 7.6 to 3.5 where wearing prosthesis at 6 months. 3 patients underwent surgical management and were considered to have failed treatment | Small sample size<br>No comparison group<br>Short follow-up time<br>No mentions as to whether there were any complications<br>Used US imaging as aid in diagnosing presence of neuroma<br>Did not measure QoL |
| Jung (2014)[13] | Shock wave therapy | Pain rating scale – resting and | RCT | 30 stump neuromas (4 lower limb amputees) | At final assessment at 3 months<br>McGill scores: ESWT 38.8±9 to | Used US in diagnosis and follow-up<br>Short follow-up<br>Did not measure effects on QoL |

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| | | active), VAS resting and active, McGill scores | | | 11.8±3.1<br>Control 37.2±7.7<br>VAS-A scores:<br>ESWT 7±1.5 to 2.8±0.8<br>Control 7.2±1.4 to 5.8±2.0<br>PRS-A<br>ESWT 46.3±12.4 to 15.8±6.0<br>Control 44.2±15.4 to 35.1±16.0 | Did not examine phantom pain<br>No complications in either group |

**Table 4: Radiofrequency treatments**

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|---|---|---|---|---|---|---|
| Zeng (2016)[25] | Coblation | VAS score | Case report | 1 AKA | Pain reduced from 8/10 to 2/10 at 6m | Anecdotal evidence<br>Examined the effects of coblation on PLP<br>Used US imaging for diagnosis and as therapy aid<br>QoL improvement briefly mentioned, not formally assessed<br>No mention of presence/ability to wear prosthesis. |

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| | | | | | | No complications reported |
| Kim (2014)[31] | Pulsed radiofrequency | VAS score | Case report | 1 AKA | Decrease in VAS for 6 months during study follow-up (8.5 to 4.5 when wearing prosthesis | Anecdotal<br>Short follow-up<br>Used steroid injection in addition to PRF<br>No mention of any complications<br>No other outcomes measured<br>No mention of concomitant phantom pain but stump pain differentiated from spinal stenosis with EMG<br>US used for diagnosis but not follow-up<br>Pain score on wearing prosthesis improved |
| Restrepo-Garces (2011)[32] | Ultrasound Guided Pulsed radiofrequency | VAS score | Case report | 1 BKA | VAS score reduced from 10 to 3 at 6 months post intervention | Low quality evidence<br>Anecdotal<br>Ability to wear prosthesis after intervention mentioned |

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| | | | | | | in results<br>US not used for follow-up<br>No complications occurred during follow-up<br>QoL not analysed<br>No mention as to whether phantom pain was present |
| West (2010)[33] | Ultrasound Guided Pulsed Radiofrequency | VAS score, ADLs, ability to wear prosthesis in painful stump neuroma, analgesic medications | Case series | 4 (all BKA or AKA) | All 4 were pain-free or had significant improvement for at least 4 months.<br>All 4 could wear prosthesis afterwards<br><br>VAS scores at 6 months<br>Case one: 9 to 4<br>Case two:8 to 0<br>Case three: 8 to 3 | Anecdotal evidence<br>Short follow-up time<br>Small sample<br>VAS not mentioned for one case<br>No complications were reported<br>QoL not analysed<br>Explored the effect on phantom limb pain in addition to stump pain. |
| Wilkes (2008)[34] | Pulsed radiofrequency | VAS score | Case report | 1 BKA | Patient was pain free for 4 months | Anecdotal<br>Case report |

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| | of sciatic nerve for stump pain and phantom pain | | | | before phantom limb returned. Unclear whether stump neuroma pain returned.<br><br>VAS average 7/10 to 0/10 at 4 months after treatment | Short follow-up<br><br>Descriptive results only - no qualitative data for measuring the pain<br>Ability to wear prosthesis after procedure not mentioned.<br>QoL not analysed<br>No mention as to whether there were any complications |
| CCSC, “Centro-central short circuit”, the procedure that describes anastomosing nerve ends to one another; AKA, above knee amputation; BKA, below knee amputation; VAS, visual analogue scale; VAS-A, visual analogue score when active; PRF, pulsed radiofrequency; TNI, targeted nerve implantation; ESWT, extra-corporeal shock wave therapy; RCT, randomised control; QoL, quality of life; US, ultrasound; PLP phantom limb pain; EMG, electromyography | | | | | | |