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Phantom limb pain: A review of evidence-based treatment options

# Tian S *et al*. Treatment options for phantom limb pain

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# Abstract

# Phantom limb pain (PLP) is not uncommon after amputation. PLP is described as a painful sensation perceived in the missing limb. Despite of its complicated pathophysiology, high prevalence of PLP has been associated with poor health-related quality of life, low daily activity and short walking distances. A prompt and effective management of PLP is essential in caring for the amputee population. Current treatments including physical therapy, psychotherapy, medications, and interventions have been used with limited success. In this review, we provided an updated and evidence-based review of treatment options for PLP.

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**Key words:** Phantom limb pain; Rehabilitation; Drug therapy; Anesthesia

**Core tip:** An evidence-based review of treatment options for phantom limb pain.

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# INTRODUCTION

Post-amputation phenomena include phantom limb sensation (PLS), phantom limb pain (PLP) and residual limb pain (RLP). PLS refers to the persistent perception of a body part even after it has been removed by amputation or trauma, whereas PLP refers to the perception of pain experienced in the missing body part. The term RLP refers to pain in the remaining limb.

PLS and PLP can occur after the amputation of any part of the body, but are most often described in the limbs[[1](#_ENREF_1),[2](#_ENREF_2)]. The incidence of PLP varies from 0% to 88% after lower extremity amputations, 51% to 72% after upper extremity amputations with increase seen in more proximal amputations. The reports of PLP after hemipelvectomy range from 68% to 88%; the incidence reported is 40% to 88% following hip disarticulation[[3](#_ENREF_3),[4](#_ENREF_4)].

The etiology and pathophysiologic mechanisms of PLP are not clearly defined. However, both peripheral and central neuronal mechanisms are likely involved. In addition, psychological mechanisms have been proposed. Several investigators have considered pre-amputation pain as a risk factor for PLP[[5](#_ENREF_5)]. Independently, none of the theories fully explains the clinical characteristics of this condition.

PLP is generally located in the distal parts of the missing limb, and is usually intermittent. The intervals of pain typically range from days to weeks, but rarely interval over months or years. Each pain attack may take from a few seconds to a few hours, sometimes days. Patients with PLP often have poor health-related quality of life, low daily activity and short walking distances[[6](#_ENREF_6)]. Therefore, a prompt and effective treatment of PLP is essential in caring for the amputee population. In this review we have included the treatment options that are currently available for PLP.

# TREATMENT OF PLP

Treatment of PLP continues to be difficult and mostly unsuccessful. Studies pertaining to the treatment of PLP do not contain large controlled clinical trials that provide definitive evidence of treatment options.

This article will review the most commonly used, evidence-based practices in treating PLP, as available through literature review. Management options for PLP fall into three general categories: Physical, Behavioral and Psychological Therapies, Pharmacotherapy, and Surgery/Interventional Management summarized in Table 1.

# *Physical, behavioral and psychological therapies*

PLP is most commonly seen in patients who are unable to use prosthesis within the first 6 mo following amputation[[4](#_ENREF_4)]. Physical therapy in preparation for the use of prosthesis has been shown successful in decreasing the patient’s PLP[[7](#_ENREF_7)].

Desensitization techniques including massaging, tapping, slapping, wrapping, and friction rubbing of the residual limb are often used to treat bothersome PLS, PLP and RLP[[8](#_ENREF_8)]. Anecdotally, many patients find that for a phantom itch, scratching the remaining leg in the same spot is helpful. However no evidence-based studies to date have supported the above treatment options. Patients frequently find that their PLP diminishes with the stimulation of using prosthesis. Kern *et al*[[9](#_ENREF_9)] researched the effect of using an electromagnetically shielding stump stocking interwoven with metal lining on PLP. The influence of a silicon liner with electromagnetically protecting properties on PLP was highly significant.

Other physical therapies commonly used for the treatment of PLP are: Transcutaneous Electrical Nerve Stimulation (TENS), repetitive Transcranial Magnetic Stimulation (rTMS), Electroconvulsive Therapy, Stress-relaxation techniques and Biofeedback.

TENS has been shown to give temporary relief to PLP[[10](#_ENREF_10)]. Finsen *et al*[[11](#_ENREF_11)] studied the effect of TENS on stump healing, and postoperativeand late PLP after major amputations of the lower limb. The prevalence of PLP after active TENS was significantly decreased after four months, but not after more than one year.

Ahmed *et al*[[12](#_ENREF_12)] studied the long-term analgesic effect of rTMS on chronic PLP. This clinical trial confirmed that five consecutive days of rTMS (20 Hz, 10 second trains, intensity 80% of motor threshold) over the motor cortex could produce long lasting pain relief in patients with PLP. The significant increase of beta-endorphin was noted in these PLP patients as a result of the treatment. On the other hand, Irlbacher *et al*[[13](#_ENREF_13)] did not observe any significant long-term effects of rTMS on pain intensity or mood compared with sham stimulation recipients. Using low-frequency and intensity electromagnetic fields, Bokkon *et al*[[14](#_ENREF_14)] reported majority (10/15) of the patients with PLP had a marked reduction in the frequency and intensity of PLP and improvement in sleep and mood.

The effect of stress-relaxation training with or without biofeedback or hypnosis has been studied on PLP[[15](#_ENREF_15)]. Investigators[[16](#_ENREF_16)] reported that in 12 of 14 patients with chronic PLP, significant improvement was noted with muscular relaxation training to disrupt the pain-anxiety-tension cycle. In this study, patients required an average of 6 treatments to produce therapeutic effect. This approach was also associated with decreased anxiety levels and increased pain relief.

Multiple psychological modalities have been attempted in managing PLP.

Mirror therapy is one of the most extensively studied techniques used to treat PLP. During mirror therapy, the patient is allowed to feel the imaginary movement of the removed body part behaving as normal bodily movement through a mirror. The mirror image of the normal body part helps reorganize and integrate the mismatch between proprioception and visual feedback of the removed body[[17](#_ENREF_17)]. Mirror therapy has primarily been used with upper limb amputations with clinically proven effect in PLP and functional improvement[[18](#_ENREF_18)], but has been attempted in patients with lower limb loss as well[[19](#_ENREF_19),[20](#_ENREF_20)]. Chan *et al*[[19](#_ENREF_19)] conducted a randomized, sham-controlled trial of mirror therapy *vs* imagery therapy involving patients with PLP after the amputation of a leg or foot where 22 patients were randomly assigned to one of three groups: one that viewed a reflected image of their intact foot in a mirror (mirror group), one that viewed a covered mirror, and one that was trained in mental visualization. Their findings showed that mirror therapy reduced PLP in patients who had undergone amputation of lower limbs. Such pain was not reduced by either covered-mirror or mental-visualization treatment.

Psychotherapy was reported to yield good results. Hypnotic suggestion of stocking-glove anesthesia may lead to a reduction in PLP[[21](#_ENREF_21)]. Investigators showed that 45% of patients were successfully hypnotized, and 35% had successful improvement in PLP. Relapses occurred soon after the discontinuation of the treatment in 34% of the patients. For cramped or mal-positioned limb sensations, hypnosis can be helpful. Under hypnosis, the patient might be able to alleviate a cramped phantom hand or move an awkwardly phantom positioned limb to a more comfortable position.

# *Pharmacotherapy*

## Antidepressants: Many randomized, controlled clinical trials have shown a beneficial effect of tricyclic antidepressants and sodium channel blockers on different neuropathic pain conditions and denervation syndromes, such as post herpetic neuralgia and diabetic neuropathy. These medications are generally considered to be effective on PLP, at least for some patients[[22](#_ENREF_22),[23](#_ENREF_23)]. Wilder-Smith *et al*[[22](#_ENREF_22)] studied 94 treatment-naïve posttraumatic limb amputees with PLP who were randomly assigned to receive individually titrated doses of tramadol, placebo (double-blind comparison), or amitriptyline (open comparison) for 1 month. Both amitriptyline and tramadol provided excellent control of PLP and RLP for the treatment- naïve patients. In contrast, another study conducted by Robinson *et al*[[23](#_ENREF_23)] evaluated 39 persons with amputation-related pain lasting more than 6 mo in a 6-wk randomized, controlled trial of amitriptyline (titrated up to 125 mg per day) or an active placebo. No significant difference was noticed between the treatment groups, thus their findings did not support the use of amitriptyline in the treatment of post amputation pain.

**Anticonvulsants:** Among anticonvulsants, carbamazepine is the most commonly used medication. Elliott *et al*[[24](#_ENREF_24)] and Patterson[[25](#_ENREF_25)] reported cases of lancinating PLP that improved with oral carbamazepine. Logan[[26](#_ENREF_26)] reported incomplete relief with carbamazepine but complete relief with chlorpromazine in longstanding PLP. However, there is no evidence suggesting that carbamazepine is effective for pain that is not of the intense, brief, lancinating type. Gabapentin is another commonly used anticonvulsant for PLP. Other than sedation, the side effects are rare. Because gabapentin has no known long-term toxicity, blood level monitoring as associated with other anticonvulsants is not required. However, the results of clinical studies on the use of gabapentin to treat PLP are conflicting. For example, Bone *et al*[[27](#_ENREF_27)] concluded that a daily treatment of gabapentin, titrated in increments of 300 to 2400 mg of the maximum tolerated dose is better than placebo in relieving PLP. No significant differences in mood sleep interference, or activities of daily living were reported. Nikolajsen[[28](#_ENREF_28)], on the other hand, found that gabapentin administered in the first 30 postoperative days, with a daily dosage gradually increasing to 2400 mg/d, does not reduce the incidence or intensity of post amputation pain. Pregablin has been rarely studied in this manner, rather in one case report indicating that duloxetine and pregabalin combined effectively controlled PLP from a below knee amputation[[29](#_ENREF_29)].

## Opioids: Opioid analgesics are not the primary options for the treatment of PLP. However, Methadone has been reported to provide effective relief from PLP at 10-20 mg per day, by Harden *et al*42. Multiple lines of evidence have demonstrated that opioids can be used safely for years with a limited risk of drug dependence[[30](#_ENREF_30),[31](#_ENREF_31)]. Patients undergoing amputation related to systemic medical diseases have a 42% 5-year survival rate; thus, the risk of opioid addiction may be weighed against quality-of-life issues[[32](#_ENREF_32)]. In a study by Wu *et al*[[31](#_ENREF_31)] therapy with morphine, but not mexiletine, resulted in a decrease of post amputation pain intensity. This treatment resulted in a higher rate of side effects, with no improvement in self-reported levels of overall functional activity and pain-related interference in daily activities.

**N-Methyl-D-Aspartate receptor antagonists:** The effects of N-Methyl-D-Aspartate (NMDA) receptor antagonists on PLP have been examined in different studies[[33](#_ENREF_33), [34](#_ENREF_34)]. Experimental and clinical literature supports the effectiveness of ketamine in blocking central sensitization via affecting the NMDA receptor[[35](#_ENREF_35),[36](#_ENREF_36)]. Studies have reported low-dose ketamine infusion to be effective in the treatment of complex regional pain syndrome (CRPS). However the effectiveness of ketamine was controversial in relieving PLP in one randomized clinical trial[[37](#_ENREF_37)]. Nikolajsen *et al*[[38](#_ENREF_38)] researched on the effects of ketamine on persistent RLP and PLP in a double blind, placebo- controlled study. In this study, Ketamine (bolus at 0.1 mg/kg per 5 min followed by an infusion of 7 micrograms/kg per min) was administered intravenously to 11 patients with established RLP and PLP. All 11 patients responded with a decrease in the rating of RLP and PLP assessed by VAS and McGill Pain Questionnaire (MPQ). Ketamine increased pressure-pain thresholds significantly. Wind-up like pain (pain evoked by repeatedly tapping the dysaesthetic skin area) was reduced significantly by ketamine. In contrast, no effect was seen on pain evoked by repeated thermal stimuli. In another study by Nikolajsen[[33](#_ENREF_33)], 19 patients received memantine, an NMDA receptor antagonist available for oral use, in a blinded, placebo-controlled, crossover fashion. Memantine failed to have any effect on spontaneous pain, allodynia, or hyperalgesia. Similar results were also found by a different study group[[34](#_ENREF_34)]. Oral dextromethorphan, another NMDA receptor antagonist, was found to effectively reduce PLP in a cancer-related amputation group[20].

**Beta-adrenergic blockers:** Beta-adrenergic blockers have also been suggested for treatment of PLP, based on three cases studies[[39](#_ENREF_39)]. However, in a double-blind cross-over trial of propranolol dosed up to 240 mg daily, the investigators were unable to show significant improvement in post-traumatic neuralgias[[40](#_ENREF_40)].

**Benzodiazepines:** The general impression is that benzodiazepines do not produce substantial pain relief, but Bartusch SL *et al*[[41](#_ENREF_41)] have reported that Clonazepam did provide effective pain relief when used on two patients with lancating PLP after total hip disarticulation.

**Capsaicin:** Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the pungent component of red peppers. Studies indicate that capsaicin, when applied topically to skin, depletes substance P from peripheral nociceptive C fiber nerve terminals, thereby increasing the threshold for, and rendering the skin area relatively insensitive to chemical and thermal stimuli. The effect of capsaicin as an alternative treatment on RLP was also tested in a case study to be effective[[42](#_ENREF_42)].

**Intravenous and epidural therapy:** A few studies were found to use intravenous therapy for PLP, although the clinical use of such treatments is not widely accepted. Ina study by Simanski *et al*[[43](#_ENREF_43)], six of eight patients (75%) had no phantom limb pain after 10 days of intravenous treatment with salmon-calcitonin (maximum of five cycles of calcitonin infusion). Patient satisfaction was examined with a numeric rating scale (NRS 1-6) between the single infusion cycles. Modifications were done to the time period or drug dosage between infusions as the result of patient satisfaction rates. This study shows good or excellent results in patient satisfaction for six of eight patients (75%) in systematic follow-up examinations after 3, 6 and 12 mo. Authors recommend a prospective randomized trial to verify the results of intravenous salmon-calcitonin in a larger population. However, in another study,[[44](#_ENREF_44)] intravenous calcitonin reduced PLP in the early postoperative period, but PLP on longer-term follow-up was not adequately controlled.

[Karanikolas](http://www.ncbi.nlm.nih.gov.proxy.lib.mcw.edu/pubmed?term=Karanikolas%20M%5BAuthor%5D&cauthor=true&cauthor_uid=22464089) *et al*[[45](#_ENREF_45)] used a randomized clinical trial to assess the effectiveness of optimized perioperative analgesia on PLP, as measured at 1 and 6 mo postoperatively, using the visual analog scale (VAS) and the McGill Pain Questionnaire (MPQ). In this study, patients received epidural analgesia or intravenous PCA starting from 48 h preoperatively and continuing 48 h postoperatively. The study concluded that using optimized epidural analgesia or intravenous PCA, starting 48 hours preoperatively and continuing for 48 h postoperatively, decreases PLP at 6 mo. Gehling *et al*[[46](#_ENREF_46)] showed that preoperative, intraoperative, and postoperative epidural anesthesia were associated with a significant reduction of PLP, 12 mo after amputation. This technique does not completely abolish PLP, but rather increases the number of patients with a milder form of PLP.

# *Interventional therapy*

## Central nervous system: Several neurosurgical procedures, including deep brain stimulation (DBS), and motor cortex stimulation (MCS) have been used to treat refractory PLP. Intracranial neurostimulation caused initial pain relief in 80% of patients with sensory thalamic stimulation[[47](#_ENREF_47)] and 86% of patients had significant relief with DBS. Thalamic stimulation may block spontaneous neuronal discharge in the brain which has been proposed to mediate phantom sensation in some models[[48](#_ENREF_48)].

Bittar *et al*[[49](#_ENREF_49)] concluded from his research that DBS has been used successfully for the treatment of PLP, with results of decreased pain, decreased opiate intake, and improved quality of life.

[Yamamoto](http://www.ncbi.nlm.nih.gov.proxy.lib.mcw.edu/pubmed?term=Yamamoto%20T%5BAuthor%5D&cauthor=true&cauthor_uid=22464089) *et al*[[48](#_ENREF_48)] concluded that inhibition of spinothalamic tract neurons, restoration of the original receptive field representation and modulation of thalamocortical rhythmic oscillations are possible mechanisms of Vc-DBS for the treatment of deafferentation pain, including PLP. Sol *et al*[[50](#_ENREF_50),[51](#_ENREF_51)] used long-term MCS in three patients with intractable pain after upper limb amputation. Functional magnetic resonance imaging (fMRI) correlated with anatomic MRI permitted frameless image guidance for electrode placement. Pain control was obtained for all patients initially, and relief was stable for two of the three patients at 2-year follow-up. Percutaneous stimulation of the periosteum has been used, even though it has not been well studied[[52](#_ENREF_52)].

SCS could produce increased inhibition in the dorsal column of the spinal cord and result in relief from PLP[[53](#_ENREF_53)]. Evaluations of SCS have shown encouraging results in neuropathic pain, including reflex sympathetic dystrophy[[54](#_ENREF_54)]. Thus, spinal cord posterior column stimulation is the most common neurosurgical technique used for the treatment of PLP. The selection process is very crucial. Response to TENS or percutaneous electrical stimulation may predict a response to dorsal column stimulation[[55](#_ENREF_55)]. Even with appropriate patient selection, investigators have reported that only 65% of patients receive a greater than 25% reduction in pain immediately after surgical implantation[[56](#_ENREF_56)]. Further, the success rate of dorsal column stimulation steadily declines over time, and a greater than 50% long-term pain reduction is present in only one third of patients who originally showed improvement. SCS may not provide any improvement in patients with severe pain and PLS.

Some investigators have reported multiple neurosurgical techniques apart from electrical stimulation, including intrathecal implantable devices, stereotactic thermocoagulation lesions, and cordotomy[[74](#_ENREF_74)]. Some of these treatments may have more serious complications than benefits[[4](#_ENREF_4)].

## Peripheral nervous system: Neural Blocks or neuroablative procedures are commonly used in the treatment of PLP. These procedures range from lumbar sympathetic trunk block, peripheral nerve block, epidural and subarachnoid blocks, to radiofrequency ablation or chemo- or neurolytic ablation of peripheral nerves. Overall the efficacy of these procedure has not been substantiated[[8](#_ENREF_8)].

Multiple trials assessed perineural[[57](#_ENREF_57)] and intraneural[[58](#_ENREF_58)] bupivacaine blocks, either at the time of surgery or immediately postoperatively. Despite some early benefits, no difference in pain was reported between the intervention and control groups in the postoperative period[[59](#_ENREF_59)]. Perineural block was similar to infusion of local anesthetic through epidural catheter[[57](#_ENREF_57)]. Evaluation of continuous brachial plexus analgesia showed prevention of the establishment of PLP, which did not reappear during follow-up of 1 year[[60](#_ENREF_60)]. Nerve sheath catheter analgesia also showed reduced prevalence[[61](#_ENREF_61)].

In a study by [Casale](http://www.ncbi.nlm.nih.gov.proxy.lib.mcw.edu/pubmed?term=Casale%20R%5BAuthor%5D&cauthor=true&cauthor_uid=22464089) *et al*[[62](#_ENREF_62)], contralateral injections of 1 mL 0.25% bupivacaine in myofascial hyperalgesic areas attenuated phantom limb pain and affected phantom limb sensation. Sixty minutes after bupivacaine injection, a statistically significant relief of phantom limb pain was observed. Bupivacaine consistently reduced/abolished the phantom sensation in 6 out of 8 patients. The clinical importance of this treatment method requires further investigation

## Musculoskeletal system: Neuromas develop in a large number of patients and not only cause RLP, but are also involved in the generation of PLP. Gruber[[63](#_ENREF_63)] studied the effects of a procedure for sclerosis of painful stump neuromas under real-time high-resolution sonographic guidance. In this study, neurosclerosis was performed on 82 patients by means of high-resolution sonographically guided injection of up to 0.8 mL of 80% phenol solution. During treatment all patients had marked improvement in terms of reduction of pain measured by VAS. Twelve (15%) of the subjects were pain free after one to three treatments, 9 of the 12 achieving relief after the initial instillation. At 6-month follow-up evaluation, 52 patients assessed their present pain quantity with a simplified three-step score. Twenty (38%) of the 52 patients reported almost unnoticeable pain, 33 of the 52 patients (64%) reported pain equal to the minimum reached during therapy, and 18 (35%) of the 52 patients had markedly decreased incidences of painful periods. The neurosclerosis procedure had a low complication rate (5% rate of minor complications, 1.3% rate of major complications). The study concluded that high-resolution sonographically guided neurosclerosis should be included in the list of recommended procedures to manage chronic PLP and RLP.

## ACUPUNCTURE

Electroacupuncture has been shown to provide relief from PLP in the arm[[64](#_ENREF_64)]. Recently Davies[[65](#_ENREF_65)] reported that a series of seven weekly sessions of acupuncture carried out on a patient’s left intact arm, provided complete relief of PLP and a considerable improvement of PLS in the patient’s above-elbow amputated right arm.

Although short-term relief has been reported with several acupuncture studies, no long-term improvement in patients with a history of nerve damage, Including PLP, has been reported[[66](#_ENREF_66)].

## NEUROTOXIN INJECTION

Botulinum toxin injections have commonly been used to treat spasticity and other hypertonic muscular diseases by selectively preventing the release of acetylcholine at the nerve-muscle junction. Recently, such injections have been used for the treatment of RLP and PLP[[67-70](#_ENREF_67)]. Kern *et al*[[68](#_ENREF_68),[69](#_ENREF_69)] injected 100 IU of botulinum toxin A in four muscle trigger points of an amputation stump and reported that the injection reduced PLP by approximately 60% to 80%. In a subsequent study[[89](#_ENREF_89)], patients who had undergone amputation of the arm (*n =* 2) or leg (*n =* 2) were treated with botulinum toxin type B injections at several trigger points of their stump musculature. As a result, all patients experienced a reduction in RLP that lasted for many weeks. Wu *et al*[[67](#_ENREF_67)] conducted a prospective randomized double-blinded pilot study to examine the effect of botulinum toxin type A injection *vs* the combination of Lidocaine and Depomedrol injection. The study consisted of 14 amputees with intractable, refractory RLP and/or PLP. Each patient was evaluated at baseline and every month after injection for 6 mo. The study found that both botulinum toxin type A and Lidocaine/Depomedrol combination injections resulted in immediate improvement of RLP (but not PLP) and pain tolerance. The treatment effect lasted for 6 months after the injection in both groups. Another case study by Jin L *et al* [[70](#_ENREF_70)] have also reported significant relief in both RLP and PLP from intramuscular and/or cutaneous injections of botulinum toxin type A

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# FUTURE DIRECTIONS OF PLP TREATMENT

PLP is a common consequence of the removal of a limb or organ. The understanding of PLP has improved substantially since the 1990s as a result of experimental studies that showed a series of morphologic, physiologic, and biologic changes resulting in hyper-excitability in the nervous system. At present, no evidence-based clinical guidelines to manage PLP are available. As we summarized above, many options were reported to manage PLP. It is important to treat each PLP patient with a tailored, individualized and sequential protocol. A multidisciplinary approach may achieve the best result. It is also advised that initial treatment should be low cost, and less invasive. The invasive treatment options should be reserved until non-invasive attempts fail.

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**Table 1 Treatment options for phantom limb pain**

|  |  |
| --- | --- |
| Physical therapies | DesensitizationProsthesis useStump stocking, Transcutaneous electrical nerve stimulation Repetitive transcranial magnetic stimulation Mirror therapy  |
| Behavioral and psychological therapies | Stress-relaxation TechniquesHypnosisElectroconvulsive therapy |
| Antidepressants | Tricyclic antidepressantsSodium channel blockersAmitriptyline and tramadol |
| Anticonvulsants | Carbamazepine, chlorpromazine, gabapentin, Combined duloxetine and pregabalin |
| Opioids | MethadoneMorphine  |
| NMDA Receptor Antagonists | Ketamine, dextromethorphan |
| Others | Beta-adrenergic blockersBenzodiazepines: ClonazepamCapsaicin creamSalmon-calcitonin |
| Central nervous system | Deep brain stimulation Motor cortex stimulation Stereotactaxis lesions, Spinal cord stimulation Intrathecal implantable devicesCordotomy |
| Peripheral nervous system | Bupivacaine blocksBrachial plexus analgesiaNerve sheath catheter analgesia, Contralateral Bupivacaine InjectionNeuroablative procedures |
| Musculoskeletal system | NeurosclerosisAcupuncture,Neurotoxin Lidocaine/Depomedrol injection |