Postamputation pain: a multidisciplinary review of epidemiology, mechanisms, prevention, and treatment

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ABSTRACT

Despite humanity's long experience with amputations, postamputation pain remains a highly prevalent, incompletely understood, and clinically challenging condition. There are two main types of postamputation pain: residual limb pain (including but not limited to the "stump") and phantom limb pain. Despite considerable overlap between the two, they also have distinct clinical features, risk factors, and pathophysiological mechanisms. Central, peripheral, and spinal mechanisms may all contribute to the protean manifestations of persistent postamputation pain; an improved understanding of these mechanisms will be essential to identify the most promising interventions for the prevention and treatment of postamputation pain. Although there are currently no standardized prevention or treatment recommendations for any type of postamputation pain, an evidence-based, multimodal strategy including pharmacological agents, nonsurgical procedures, surgery, complementary and integrative techniques, and assistive technologies may prevent the development of chronic postamputation pain after amputation and/or optimize treatment outcomes.

INTRODUCTION

Amputations predate recorded human history. A recent report in *Nature* describes evidence of a lower extremity amputation over 30,000 years ago.[1] Published cases of amputations in Neanderthals remain inconclusive, but evidence suggests that our closest relatives were more sensitive to pain than Homo sapiens[2] so the experience of postamputation pain likely goes back even farther into prehistory. Postamputation pain has almost certainly plagued mankind for as long as amputations have existed.

There are over 2.5 million amputees in the USA, with over 85% of cases secondary to diabetes or vascular disease.[3] In diabetics, the annual incidence of amputation is around 4 per 1000, being higher in males, African Americans, veterans, and those with multiple medical comorbidities.[3] In Medicare patients with peripheral vascular disease, the annual amputation rate approaches 6%.[3] Worldwide, the annual incidence of traumatic amputations ranges between 1.5 and 2 per 1000 people, being highest in Southeast Asia, African Americans, and males in their early 20s.[4] The leading causes of traumatic amputations are exposure to mechanical forces (eg, farm accidents), falls (the most common cause in the elderly), motor vehicle collisions and conflict. Over two-thirds of traumatic amputations involve the upper extremities, especially the fingers.[4]

The socioeconomic costs of amputations are staggering. Life expectancy is lower in amputees than non-amputees, and quality of life is severely diminished in major limb amputees, especially those with leg amputations.[4 5] These burdens arise not only from the high prevalence of comorbidities (eg, systemic illness, traumatic brain injury and post-traumatic stress disorder in wartime amputations) but also from the deleterious effects of chronic pain (eg, chronic inflammation, psychopathology, maladaptive lifestyle changes), with studies showing higher rates of psychopathology and mortality in individuals with other forms of deafferentation pain compared with those with similar injuries who are devoid of pain.[6]

The direct financial costs of postamputation pain are difficult to separate from those related to disability associated with limb loss, but one study estimated hospitalization costs exceeded US$8.3 billion in the USA for amputations in 2009 dollars.[3] In another study, the lifetime cost of a lower extremity amputation was estimated to approach US$900,000 in 2019 dollars.[7] Pain is a major reason for health-related quality of life decrements after amputation (eg, inability to use a prosthetic), with studies reporting return-to-duty rates ranging between 11% and 47% among military personnel, and a 42% disability rate in civilian lower extremity amputees.[7–9]

Postamputation pain is not a disease; it is a syndrome representing a constellation of signs and symptoms, with different etiologies and mechanisms, an absence of pathognomonic biomarkers, and a wide-ranging response to treatment. Because mechanism-based treatment of pain is believed to be more effective than disease-based therapies,[10] treatment of postamputation pain must be empirical, based on clinical data regarding individual pathophysiology, rather than solely contingent on the causative event (amputation). This review provides an overview of the diagnosis, risk factors, and mechanisms of postamputation pain, and discusses evidence-based strategies for its prevention and treatment.

DIAGNOSIS AND CLINICAL FEATURES

Broadly, pain associated with the loss of a limb can be considered postamputation pain. There are two distinct categories of postamputation pain: phantom limb pain and residual limb pain. Phantom limb pain denotes painful sensations referred to the absent limb while residual limb pain is localized to the extant limb, including (but not limited to) the stump itself. Phantom limb pain is more neuropathic in nature and commonly associated with functional changes in the peripheral and central somatosensory systems,[11 12] although phantom limb pain may also be referred from lesions more proximal to the amputation, such as radiculopathy, neuroma, or musculoskeletal sources.[13] By contrast, residual limb pain tends to be more nociceptive, and it includes pain due to tissue injury (eg, amputation trauma, wound infection, foreign body/shrapnel, pressure ulcers, prosthetic irritation, and ischemia), heterotopic ossification, and direct or referred spinal or peripheral joint pain related to altered biomechanics.[13–16] Residual limb pain can also result from neuromas or nerve damage above the amputation,[17] causing neuropathic pain.

Although the category of postamputation pain can be discerned from patient localization, appropriate management requires the identification of underlying causes through history and physical examination, as well as consideration of diagnostic studies.[12] Phantom limb pain and residual limb pain are usually present concurrently, with many amputees reporting features of both. Notably, nociplastic pain may also be present in both postamputation pain types, as well as other related pain syndromes spreading beyond the anatomic region of the amputation (eg, complex regional pain syndrome (CRPS), post-traumatic fibromyalgia).[15]

RISK FACTORS

Limb amputations occur in otherwise healthy, young soldiers and civilians injured in military conflicts or industrial accidents, as well as elderly patients with multiple comorbidities including diabetes or vascular disease. The disparate demographic characteristics and biopsychosocial contexts make it difficult to identify specific risk profiles, especially since there are multiple types of postamputation pain that arise through various pathophysiological pain mechanisms following amputation. However, both historical and modern epidemiological studies of postamputation pain provide insights regarding general characteristics that influence the likelihood that an amputation will result in chronic postamputation pain.

Well-known risk factors for postamputation pain include patient-related factors (age,[18–20] socioeconomic factors,[19 20] genetics,[21] psychopathology,[20–23] smoking[20]) and amputation-related factors (degree of trauma,[20] location of amputation,[18 19 21] surgical approach,[21] preoperative and postoperative pain,[11 18 21 24] anesthetic technique[19 22 24]); these are summarized in box 1.[11 18–25] The presence and severity of preamputation pain correlate with the presence and severity of phantom limb pain and residual limb pain.[24 26] Pre-existing pain states may also lead to phenomena contributing to central sensitization (eg, alterations in neuronal excitability, impaired spinal and supraspinal pain inhibition pathways), which predispose an individual to postamputation pain.[13 18] Similarly, severe acute pain immediately following amputation is predictive of chronic postamputation pain.[20 25 26] Pre-existing psychological factors such as post-traumatic stress disorder, depression, catastrophizing, and anxiety, are also associated with postamputation pain.[22 23]

Box 1 Risk factors for postamputation pain[11 18–25]

Young age.
Degree of trauma.
Location of amputation.
Socioeconomic factors.
Psychopathology.*
Genetics.
Surgical approach.*
Preoperative and severe postoperative pain.*
Anesthetic technique.*
Smoking.*

*Potentially modifiable risk factors.

MECHANISMS

Since residual limb pain is mechanistically more similar to traditional post-traumatic and postsurgical pain, the discussion of postamputation pain mechanisms will focus primarily on phantom limb pain. The non-intuitive nature of phantom limb pain has made it a subject of great interest both within and outside of medical science. How, exactly, does one feel pain from a body part that no longer exists? Despite decades of work on this topic, the mechanisms underlying phantom limb pain and other types of deafferentation pain remain incompletely understood, but key contributors are thought to include functional and organizational changes in the central nervous system (CNS), peripheral nervous system pathology, and their interplay.

Many parts of the brain and spinal cord exhibit somatotopic organization of sensory inputs and motor outputs. Reorganization of these somatotopic maps, especially within brain cortices, is a common finding in phantom limb pain.[27–30] For example, functional MRI (fMRI) following upper limb amputation has revealed an expansion of activity evoked by tactile stimulation of the lips into cortical areas that previously encoded the hand, with the magnitude of this shift correlated to phantom limb pain intensity.[31] Similar ectopic expansion of receptive fields has been observed in nonhuman primates following digit amputation[32] or deafferentation by dorsal rhizotomy.[33] Changes in representational maps have also been identified in the thalamus, both upstream and downstream of cortical reorganization events.[28 30] However, the precise neurobiological changes and how those relate to the clinical presentation of phantom limb pain remain incompletely understood.

Several methodological variables in mapping studies contribute to this complexity. The techniques used to evoke brain activity in studies (eg, by phantom limb movements, imagery of phantom limb movement, or mirror image movement of the contralateral limb) differ, and how brain regions are defined also vary.[29] Another consideration is the recording technique used to generate maps, which reflect different aspects of brain activity. In non-human primates, fMRI and local field potential measurements do not always correspond to multiunit recordings of spiking activity.[34] These disparities likely reflect differential effects of deafferentation on subthreshold activity versus action potential firing at the circuit level; anesthesia, which is often used in such animal studies, may further confound measurements.[34] Lastly, cortical representational maps and their changes following deafferentation vary across stimulus modalities. Cortical maps of innocuous touch and temperature nociception, and their respective changes following deafferentation, do not strictly coincide; they also exhibit distinct interareal circuitries.[34] Such stimulus-specific

changes could lead to contradictions between studies, even in the setting of identical underlying biological substrates.

Despite these considerations, there is a consensus that a quantitative relationship exists between phantom limb pain intensity and cortical reorganization, although the specific cause-and-effect vectors in that relationship remain enigmatic, and some studies have shown that phantom limb pain correlates with an absence of cortical reorganization (ie, a persistent disparity exists between a missing body part and its cortical representation).[6] One conceptual model is the "neuromatrix theory", which posits that major deafferentation exceeds the limits of biological plasticity of the CNS to reconcile the changed pattern of inputs resulting in maladaptive pain perception referred to the missing limb.[30 35] This pain can be exacerbated by mismatches between somatosensory inputs, visual feedback, and rearranged cortical representation maps.[28 36] Another concept espoused is that of proprioceptive or pain "memories" in the CNS, such that either the position of the limb before amputation or pain experiences contemporaneous with amputation result in a cognitive recollection of feelings evoked by movement, or imagery of movement, of the residual limb. Such sensations might be protracted by the patient's inability to receive visual feedback that the limb is restored to a nonpainful position.[30 37] Whereas these models describe potential connections between phantom limb pain and cognitive experiences such as sensory input and memory, the mechanistic links between phantom limb pain and altered brain representative maps remain unknown.

One compelling potential mechanism linking phantom limb pain and cortical reorganization involves collaboration between the central and peripheral nervous systems. In this model, input from neurons innervating the residual portion of an amputated limb might produce pain referred to the missing limb by inappropriately activating the reorganized cortical or thalamic regions formerly representing the lost limb.[28 30] Such input may arise from neurons residing in the neuromas at the truncated ends of transected nerves and/or from adjacent spared neurons that innervate residual limb tissue. Both populations of neurons have been shown to exhibit spontaneous firing following peripheral nerve injury[38 39] and might contribute not only by delivering ectopic afferent inputs to circuits involving the spinal cord and brain but also by sensitizing these circuits. One problem with this model is that there is a distinction between patient perceptions of phantom limb pain and residual limb pain, with the two types of pain often exhibiting distinct time courses.[30] Another argument against peripheral neurons being primary drivers of phantom limb pain stems from the lack of definitive evidence for the long-term efficacy of continuous regional nerve blockade in the amputated limb. Although some studies suggest at least temporary efficacy,[40] others do not, with most limited in quality.[28 30 41] However, these limitations also make it premature to exclude the mechanistic contributions of peripheral input to the initiation or maintenance of phantom limb pain. It is also worth noting that other parts of the peripheral nervous system may play a role, such as more proximal parts of transected neurons or sympathetic neurons.[42]

Finally, in addition to peripheral and supraspinal mechanisms, the spinal cord dorsal horn may be an important contributor to phantom limb pain. It is within the dorsal horn where inputs to peripheral sensory neurons are transmitted to pathways projecting to the brain, serving as a site of substantial somatotopically organized processing of nociceptive and non-nociceptive input, as well as an important target of descending pain modulatory pathways. Neuronal and non-neuronal cells in the dorsal horn exhibit dynamic changes at molecular and anatomical levels in response to peripheral nerve injury, resulting in changes in neuronal excitability, inhibitory interneuron tone, and spontaneous firing,[43 44] all of which may dramatically alter relationships between peripheral inputs and outputs to the brain, thus shaping pain perceptions (figure 1).

PREVENTION

Although many studies have reported on the utility of various pharmacological, procedural, and/or physical treatments in the management of acute postamputation pain, no specific anesthetic technique or perioperative analgesic regimen has been reliably demonstrated to prevent the development of chronic postamputation pain.[12 21 45 46] Pharmacological treatments used to manage postamputation pain have also been studied as pre-emptive analgesics to prevent postamputation pain. Although anticonvulsants such as gabapentin are widely used to treat phantom limb pain, perioperative gabapentin has not been demonstrated to prevent phantom limb pain.[21 47 48] There has also been substantial interest in ketamine to prevent postamputation pain, given its N-methyl-D-asparate (NMDA)- receptor antagonism and the role of these receptors in the development of central sensitization. However, one randomized controlled trial (RCT) evaluating the addition of perioperative ketamine infusion to standard patient-controlled analgesia (PCA) postoperatively did not find significant differences in the prevention of chronic phantom limb pain.[49] Another study evaluating epidural ketamine plus bupivacaine versus epidural saline and bupivacaine for lower limb amputation surgery found that epidural ketamine provided significantly better short-term analgesia, but rates of persistent postamputation pain at 12 months were similar (and low) for both groups.[50] Notably, safety concerns with neuraxial administration of ketamine have precluded general acceptance of this treatment.[21 48]

As with pharmacological agents, regional techniques have at best a modest impact on the incidence of chronic postamputation pain. Most studies evaluating peripheral nerve blocks in amputation are small, unblinded, and/or retrospective in nature, without long-term follow-up to assess prevalence.[21] One recent study randomized 80 patients to receive 96 hours of perineural local anesthetic infusion via catheter placed during surgery or placebo, finding no significant differences in long-term phantom limb pain or residual limb pain, although the authors acknowledged that the study was underpowered with low overall rates of phantom limb pain and residual limb pain in their population.[51] For epidural analgesia, nearly a dozen randomized or retrospective studies have been mixed in finding significant differences in long-term postamputation pain outcomes compared with placebo or a perineural catheter.[13 21 46 50 52–54] One RCT found that compared with controls receiving general anesthesia and conventional analgesia, perioperative epidural analgesia or intravenous PCA were associated with decreased phantom limb pain 6 months after amputation, but no significant differences in residual limb pain were observed.[54] Although the results are mixed, studies that initiated epidural anesthesia more than 24 hours before surgery, and those that have compared epidural analgesia to suboptimal perioperative pain regimens, have yielded better results at preventing postamputation pain.[6 13] These observations highlight the importance of preoperative pain, as well as painful intraoperative events and postoperative pain, in the development of postamputation pain.

Given the strong correlation between perioperative pain and chronic postamputation pain, as well as the postulated mechanisms of chronic postamputation pain pathogenesis discussed

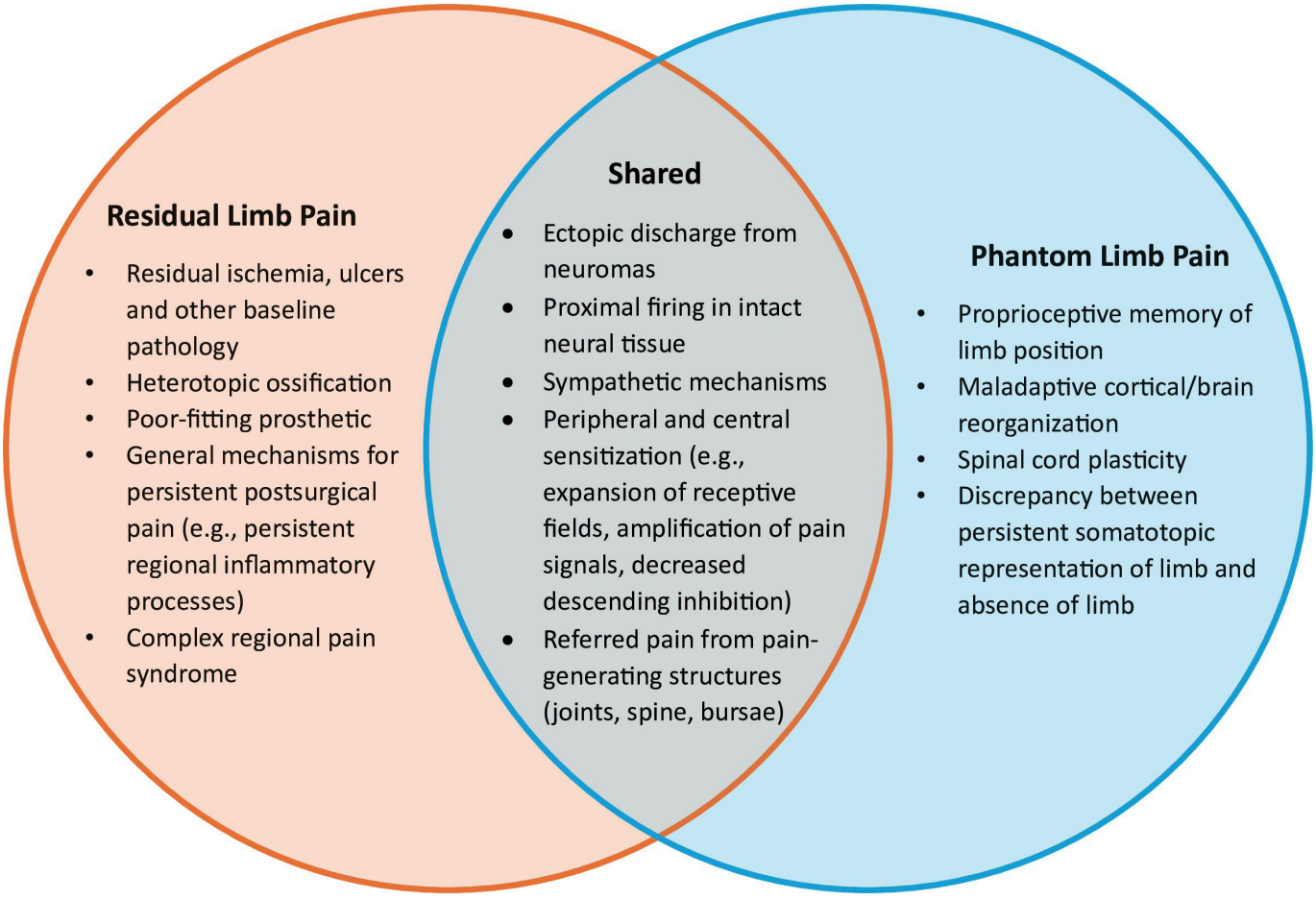

Figure 1 Distinct and overlapping mechanisms of residual and phantom limb pain.* *Denotes main form of postamputation pain presentation as there is likely overlap between all putative mechanisms for residual and phantom limb pain.

above, it is both puzzling and discouraging that pre-emptive analgesic techniques have not consistently demonstrated significant advantages in long-term postamputation pain outcomes. These findings are not unique to amputations and have been observed in many other studies evaluating preventive analgesia for chronic postsurgical pain.[55–57] One explanation may be the high degree of heterogeneity within the surgical population, which is particularly true for the population of patients undergoing amputation. In addition, the sheer range of potential pharmacological and procedural options, along with variations in dosing regimens, techniques and the conventional paradigm of multimodal analgesia, make it difficult to establish superiority for any single intervention. Lastly, the timing and duration of perioperative analgesic interventions are often limited to the immediate postoperative period. It may be that treatments initiated earlier (or even preoperatively) and continued longer postoperatively would yield better long-term outcomes, which is consistent with the previous observations of epidural analgesia for the prevention of chronic postamputation pain.[6 13]

In addition to acute postoperative pain, postamputation complications may influence the development of postamputation pain, with different complications associated with different types of postamputation pain. Neuromas are associated with neuropathic phantom limb pain and residual limb pain, whereas infection, heterotopic ossification, and poor prosthetic fit are more associated with residual limb pain.[22] Notably, the presence of residual limb pain is an independent risk factor for the development of phantom limb pain regardless of residual limb pain etiology, suggesting shared mechanisms.[19 58]

TREATMENT

Pharmacological treatments

Pharmacotherapy is considered a mainstay of treatment for postamputation pain, especially phantom limb pain. However, a 2016 Cochrane review found that in this patient population, outcomes on pain, function, mood, sleep, quality of life, and similar measures were unclear due to most studies being small and of poor quality.[59]

Anticonvulsants, principally gabapentin and pregabalin, are first-line therapies for neuropathic pain. A 2002 randomized, double-blind, placebo-controlled, cross-over study by Bone *et al* reported on gabapentin versus placebo in 14 individuals with phantom limb pain.[60] After 6 weeks, gabapentin monotherapy was better than placebo in relieving phantom limb pain, but there were no significant differences in functional or psychological outcomes, and the study did not track longer-term outcomes.[60] Although the literature on pregabalin in postamputation pain is anecdotal, its mechanisms and efficacy for postamputation pain are presumed to be similar to gabapentin.

Antidepressants such as tricyclics (eg, amitriptyline, nortriptyline) and serotonin-norepinephrine reuptake inhibitors (eg, duloxetine, milnacipran) are first-line treatments to manage neuropathic pain. Although amitriptyline was the only pharmacological treatment recommended for phantom limb pain in a

recent expert consensus,[61] it was acknowledged that the evidence for its use is not robust, with only one amitriptyline study in the 2016 Cochrane review meeting inclusion criteria.[59] This study found no significant difference between amitriptyline versus active placebo (benztropine) for phantom limb pain, although the study was only 6 weeks in duration, and the study was not powered to detect small treatment effects.[62] An earlier study did note some efficacy for open-label amitriptyline (vs double-blind tramadol and placebo) in treatment-naïve patients with postamputation pain.[63] One randomized placebo-controlled crossover trial in central pain, including 28 with phantom limb pain, found efficacy for clomipramine and (to a lesser extent) nortriptyline.[64] Despite limited evidence, antidepressants are frequently recommended and prescribed for postamputation pain, based on their efficacy in similar pain conditions and clinician experience. A 2023 Cochrane review of antidepressants for chronic pain management found that the serotonin-norepinephrine reuptake inhibitors duloxetine 60 mg daily, and potentially milnacipran, were moderately efficacious across outcomes such pain intensity and mood, with a favorable adverse effect profile.[65]

Several studies have evaluated the use of local anesthetics to manage postamputation pain. In a randomized double-blind, active-placebo-controlled, cross-over trial comparing the short-term analgesic effects of intravenous morphine and lidocaine infusions on postamputation pain, Wu *et al* found residual limb pain was diminished both by morphine and lidocaine, while phantom limb pain was diminished only by morphine.[66] In preliminary results of a double-blinded cross-over study in eight lower limb amputees with phantom limb pain, Casale *et al* reported on contralateral injections of 1 mL 0.25% bupivacaine in myofascial hyperalgesic areas versus saline.[67] Bupivacaine injected in the healthy limb consistently reduced/abolished the phantom sensation in six out of eight patients, which was not observed in the saline patients, suggesting a systemic effect of the medication.[67] In both studies, follow-up was 1 hour or less; given the short duration of action of intravenous local anesthetics, its utility in the treatment of chronic postamputation pain is likely limited.

Due to the role of the NMDA receptor in neuronal hyperexcitability and sensitization, NMDA receptor antagonists such as memantine, dextromethorphan, and ketamine have been investigated for postamputation pain. Ketamine is commonly used for perioperative pain management and provides short-term pain relief immediately following amputation, but its role in the treatment of chronic postamputation pain is less clear.[48 59] In a randomized, double-blind, cross-over study in 20 chronic phantom limb pain patients, Eichenberger *et al* reported significantly decreased pain and a greater proportion of responders in patients receiving ketamine infusions compared with those receiving placebo and calcitonin 48-hours post-treatment.[68] There are also two small placebo-controlled trials by the same group of investigators showing benefit for dextromethorphan for phantom limb pain, and several negative randomized trials for memantine.[59]

Opioids are frequently used for acute postamputation pain management, but they are generally not recommended for chronic pain management due to their safety risks, especially in a population with a high psychiatric coprevalence rate. Evidence for their benefit in chronic postamputation pain is limited. However, given the refractory nature of postamputation pain, opioids may be a consideration in selected patients with postamputation pain who have failed other treatment modalities. A double-blinded crossover study in 12 patients by Huse *et al* found that high-dose oral morphine (70-300 mg/d) significantly decreased pain intensity compared with placebo through 4 weeks, and brain MRI of three patients showed initial evidence for reduced cortical reorganization with morphine concurrent with the reduction in pain intensity.[69] However, at 1-year follow-up, slightly more than 50% who remained on morphine continued to report substantial (>50%) pain relief.

Injections and percutaneous procedures

Injectable medications studied or used clinically for residual limb pain and phantom limb pain include corticosteroids, local anesthetics, dextrose, saline, botulinum toxin, and etanercept. Other percutaneous therapies (excluding neuromodulation discussed elsewhere in this article) include pulsed radiofrequency, radiofrequency ablation, chemical neurolysis, and cryoneurolysis. Despite the increasing options available to pain medicine practitioners, the evidence supporting clinical use for any specific treatment remains sparse.

A recent literature review of percutaneous treatments for residual limb pain or phantom limb pain by Sperry *et al* revealed only eight studies examining this topic, including six case series and two RCTs that met inclusion criteria.[70] One study involved peripheral nerve stimulation (PNS), as discussed elsewhere, and the other RCT evaluated botulinum toxin and lidocaine/methylprednisolone injected into tender muscular and non-muscular tissue.[71] The latter was a double-blinded study evaluating 14 patients with residual limb pain or phantom limb pain over 6 months. Both treatments improved residual limb pain at 6 months, but not phantom limb pain. The other studies reviewed were observational, showing a trend for more significant although modest pain relief in residual limb pain compared with phantom limb pain. A notable observation across most studies was that single injection blocks can improve pain beyond local anesthetic neural blockade duration.

A large (n=144) randomized, placebo-controlled, multicenter study evaluated a 6-day ambulatory continuous perineural local anesthetic infusion for phantom limb pain.[72] The authors hypothesized that continuous perineural blockade could have a more significant effect than a single-shot block for targeting spinal and supraspinal neural pathways responsible for cortical reorganization. Their results showed a statistically significant improvement with local anesthetic compared with placebo at 4 weeks in the double-blind phase for both phantom limb pain and residual limb pain, and lower phantom limb pain and residual limb pain scores at the 6-month open-label follow-up compared with placebo patients who did not cross over; at 12 months, there were small differences favoring treatment for residual limb pain but not phantom limb pain.[72] In a small (n=4) pilot study, lumbar sympathetic blocks compared favorably to sham-controlled dry needling/needle placement without anesthetic through 3-month follow-up, suggesting the possibility of a sympathetically mediated component to residual limb pain and phantom limb pain.[73]

Other procedures, including neurolysis, pulsed radiofrequency, and radiofrequency ablation, are limited to case series[70 74]; however, one recent multicenter RCT evaluating ultrasound-guided cryoneurolysis against a sham procedure showed no significant difference at 4 months in either phantom limb pain or residual limb pain.[75] Through post hoc analysis, the authors suggested that cryoneurolysis effectiveness may depend on the level of amputation, as transtibial amputation patients did have improvement. Overall, percutaneous injection and radiofrequency treatments may have a role in treating residual limb pain and phantom limb pain but more research is necessary.

Surgical treatments

Injury to a peripheral nerve can lead to axotomy, with distal Wallerian degeneration and proximal axonal sprouting. If the axons are unable to reach a target, the sprouts form a tangle, and in conjunction with fibroblasts, a neuroma. In limb amputation, because nerve transection is required and the target tissue no longer exists, neuroma formation is almost guaranteed. Neuroma pain, occurring in more than 50% of limb amputations, is felt in the sensory distribution of the nerve, resulting in phantom limb pain and residual limb pain.[22]

Surgeons have long tried to prevent and treat painful neuroma formation. Traction neurectomy is performed by pulling the nerve distally, transecting the nerve and allowing it to retract into the limb. Axonal sprouting still occurs, however, often resulting in a painful neuroma.[76] Nerves can be implanted into various tissues (bone, vein, muscle) to decrease the size of neuroma or place it in a quiescent environment. Although a neuroma still forms, the incidence of painful neuroma is less. Various neural toxins have been applied to nerve endings to halt neuroma formation, with little success.[77]

Providing a target for regenerating axons to reinnervate can reduce neuroma formation. Placing the nerve stump into already innervated muscle will not result in neurotization of the muscle, which can result in a painful neuroma.[78] Denervated muscle is, therefore, preferable as a target for regenerating axons, and placement of such a muscle graft over the nerve stump can prevent neuroma formation. This technique, known as regenerative peripheral nerve interface (RPNI), was developed to amplify neural signals in the form of electromyographic activity and provide better control of prosthetics. RPNIs refer to denervated sections of muscle that allow direct neurotization from the nerve stump.[79] Since a muscle graft lacks blood supply, it will revascularize from the wound bed, although at least some fibrotic muscle resorption occurs.[80] An alternative is to provide a vascularized denervated muscle target for regenerating axons from the proximal nerve stump.[81] Although randomized trials are lacking, one retrospective matched-control study reported a decreased incidence of both symptomatic neuroma formation (0% vs 13.3%) and phantom limb pain (51.5% vs 91.1%) with RPNI compared with conventional surgical therapy at an average 1-year follow-up.[82] As treatment for existing postamputation pain, two retrospective studies reported reductions in neuroma pain and phantom limb pain by 75%–85% and 45%, respectively.[83]

In targeted muscle reinnervation (TMR), the proximal nerve stump is transferred onto a normal distal motor branch. By transferring cut nerves into nearby muscles, these muscles act as signal amplifiers that can be used to control bionic prosthetics. In one small, randomized trial (n=28), TMR reduced phantom limb pain at 1 year by over 95% (3.2 vs −0.2 points on a 0–10 scale), and residual limb pain by almost 70% (2.9 vs 0.9) compared with conventional therapy.[84] As prophylactic therapy, numerous studies have reported phantom limb pain in the range of 20%–25%, and residual limb pain rates around 50% after TMR, lower than reported rates with traditional surgical amputations.[83]

Spinal cord stimulation to treat neuromas and phantom pain is widely used, with little supporting efficacy data.[85] The mechanism of action was initially thought to be stimulation of sensory fibers in the dorsal columns blocking ascending nociceptive input, but other mechanisms such as enhancement of gamma amino-butyric acid inhibition and reduction of neuroinflammation and central sensitization are likely to also contribute. In one systematic review that included 12 low-quality studies, only 7 reported significant relief of phantom limb pain at variable (3 months to 7 years) follow-up.[85] Although dorsal root ganglion stimulation has been touted to provide better relief than dorsal column stimulation for some neuropathic pain conditions, a recent review based on very low-quality studies (n=5 studies, 25 patients) found significant relief occurred in only 60% of patients.[86]

PNS involves the stimulation of 1 or 2 nerves to elicit paresthesia in lieu of pain in the distribution of the treated nerves. A systematic review (n=13 studies) that included 2 randomized trials (one sham-controlled and the other that compared PNS as an add-on to standard medical therapy) found that PNS, even when applied for only 60 days via temporary implants, reduced phantom limb pain, residual limb pain and opioid consumption, and improved quality of life for over 6 months.[87]

Table 1 Levels of evidence for treatment and prevention of postamputation pain[6 13 46 48 59 61 102]

Type of postamputation pain	Level I	Level II	Level III	Level IV	Negative
Treatment of phantom limb pain	(None)	► Gabapentin ► Transcranial direct current stimulation (short-term benefit)	► Tricyclic antidepressants ► NMDA receptor antagonists (ketamine and dextromethorphan) for short-term benefit ► Peripheral nerve stimulation ► Prolonged local anesthetic infusion ► Targeted muscle reinnervation surgery ► Opioids	► Calcitonin ► Repetitive transcranial magnetic stimulation (short-term benefit) ► Mirror therapy and virtual reality (short-term benefit) ► Regenerative peripheral nerve interface surgery ► Neurolysis of painful neuroma	► Intravenous lidocaine ► Botulinum toxin ► Sympathetic blocks (provide only immediate-term relief)
Treatment of residual limb pain	(None)		► Intravenous lidocaine (immediate-term benefit) ► Prolonged local anesthetic infusion ► Targeted muscle reinnervation surgery	► Regenerative peripheral nerve interface surgery ► Neurolysis of painful neuroma	► Botulinum toxin ► Sympathetic blocks (provide only immediate-term relief)
Prevention of postamputation pain	(None)		► Targeted muscle reinnervation surgery ► Patient-controlled opioid analgesia	► Epidural anesthesia placed >24 hours before surgery (including with calcitonin) ► Catheter-based regional anesthesia ► Regenerative peripheral nerve interface surgery ► Ketamine infusion	► Gabapentin ► Stump wrapping/limb cover (eg, aluminum foil)

Levels of evidence based on modified Oxford Centre for Evidence-based Medicine Levels of Evidence criteria.[6 103] I=systematic review of randomized trials or n-of-1 trials, II=randomized trial(s) or observational study(ies) with dramatic effect, III=non-randomized controlled cohort/follow-up study(ies), IV=case-series, case–control studies, or historically controlled studies. Note that levels may be downgraded on the basis of study quality, imprecision, indirectness, inconsistency between studies, or small absolute effect sizes.

Deep brain and motor cortex stimulation are invasive neuromodulatory techniques that have been employed as last-resort treatments for refractory, debilitating pain. In one systematic review involving 8 studies (5 prospective, n=55), between 50% and 100% of deep brain stimulation patients reported at least 50% pain relief after 1 year while the results of motor cortex stimulation were generally disappointing. In an accompanying survey of neurosurgeons, while there were mixed reviews of deep brain stimulation, most perceived motor cortex stimulation as ineffective.[88]

Complementary and integrative techniques

Complementary and integrative techniques offer promising treatment options for patients with postamputation pain. Mirror therapy is a commonly used adjunct in amputees, which exploits the brain's preference to prioritize visual feedback over somatosensory/proprioceptive feedback to improve pain. Xie *et al* performed a meta-analysis of 10 RCTs and found a statistically significant decrease in phantom limb pain in the mirror therapy group versus control within 1 month.[89] Interestingly, the authors reported that the evidence did not show that mirror therapy had long-term effects but acknowledged that may have been a byproduct of limited data.[89] A separate systematic review from Guémann *et al* concluded that mirror therapy did not reduce phantom limb pain and disability in amputees, noting the low methodological quality and lack of statistical power in the included studies.[90]

Biofeedback uses tools such as surface electromyography, electroencephalography, and/or fMRI to allow for operant conditioning and feedback learning to train patients to control typically involuntary body physiology. A systematic review on neurofeedback for chronic pain found generally positive results; although none evaluated postamputation pain, neurofeedback appears to have a low risk of harm and the potential for improving pain and other outcomes in individuals with chronic pain.[91] Similarly, other complementary and integrative techniques for postamputation pain, such as hypnosis and other mind-body therapies, lack sufficient evidence to judge their efficacy, but are safe and inexpensive.[92]

Assistive technologies

Medical innovation is developing rapidly, but relatively few assistive technologies (AT) have been studied or are available commercially for treating residual limb pain or phantom limb pain.[93] Some of the well-known AT include transcutaneous electrical nerve stimulation (TENS), transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), virtual reality (VR), and various liners/prostheses.

In a systematic review, Haito *et al* identified three studies evaluating TENS or tDCS for phantom limb pain when they excluded case series, cohort, and most retrospective studies.[94] One study evaluated 28 patients who received ten minutes of auricular TENS compared with placebo, with a modest reduction in pain in the TENS group; however, the duration of effectiveness beyond 10 min was not evaluated.[95] The second randomized study involved eight patients with primarily lower limb amputations who were treated with tDCS or placebo.[96] The authors reported a more significant improvement in the tDCS group compared with placebo but did not assess effectiveness beyond 1 week.[96] The remaining study, a retrospective evaluation of twenty patients with limb loss, showed a positive effect in treating phantom limb pain by applying TENS to the contralateral limb.[97] Although anecdotal, there are also case series reporting short-term alleviation of residual limb pain with TENS.[98]

A systematic review by Corbett *et al* identified three randomized trials evaluating rTMS for phantom limb pain, reporting mixed results.[88] One sham-controlled trial was negative, a quasi-randomized trial found a large treatment effect, while the largest study (n=54) reported only mixed, short-term (15 days) benefit. Overall, the study designs and short-term outcome data diminish any clinical inferences regarding electrical stimulation for postamputation pain.

Although adequately powered RCTs remain limited, VR is another technological area that can potentially treat postamputation pain. Rajendram *et al* performed a systematic review and meta-analysis evaluating mirror therapy and VR in alleviating phantom limb pain.[99] Only seven VR studies (n=86) met the inclusion criteria, which consisted of RCTs or cohort studies. They concluded that both VR and mirror therapy are effective for treating phantom limb pain, with no significant differences between the treatments. However, significant methodological flaws in the studies made generalization difficult.

Liners and prostheses for postamputation pain relief hold promise, as fMRI studies evaluating myoelectric prostheses' cortical effects[100] and case reports of implantable microelectrodes for sensorimotor or haptic feedback, support a positive effect on phantom limb pain.[101] The mechanisms for phantom limb pain relief include purposeful sensorimotor reintegration with subsequent "embodiment" of the prosthesis. Whereas these developments hold promise, further research is necessary to develop and improve the human prosthesis interface to include effective pain modulation.

FUTURE OPPORTUNITIES AND CONCLUSIONS

Postamputation pain is a heterogeneous condition encompassing a wide range of features that can occur following limb amputation. Although treatment remains challenging, there are a growing number of pharmacologic, interventional, surgical, and complementary techniques that may be used to prevent and manage postamputation pain (table 1). Understanding the myriad underlying risk factors and pathophysiological mechanisms that lead to postamputation pain can inform the optimal multimodal treatment strategy to prevent and treat pain after amputation.

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