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Chapter

Amputation Pain Management

Melinda S. Seering and Sangini Punia

Abstract

Considerable number of new amputations yearly in the United States and internationally represent considerable population experiencing pain that is not just acutely from surgical insult but chronically that is related to phantom limb pain and residual limb pain. This chronic pain can last from weeks to years in these patients and lead to other debilitation such as depression, anxiety and even opioid addiction. Early interventions help lessen long-term pain for these patients. These interventions include nerve blockade as well as multi-modal therapy. Understanding the pathophysiology of the pain experienced by these patients will better allow any provider to care for these patients effectively and help alleviate chronic pain in the long term.

Keywords: amputation, phantom pain, neuropathic pain

1. Introduction

Patients with amputations can be found living fulfilled lives. We have all seen them running marathons, in the Olympics, surfing, climbing Mount Everest and even as an MLB pitcher. However, most just want to lead normal lives and be the best parents, siblings, friends, or co-workers they can be. They want to return to their job and function in their daily lives as they did before. Recovery from an amputation is not immediate and takes significant time. Recovery time from amputation is usually prolonged. Wound healing is done in 4–8 weeks, but the prolonged mental, emotional, and physical recovery afterwards takes much longer and will be different for everyone. One of the limiting factors for recovery from an amputation is pain.

In looking at data from the Amputee Coalition, there are 185,000 in the United States every year. This means that an average of two million people is living with an amputated extremity in the United States alone [1–3]. Other data to consider is just as alarming; globally, there are 1 million amputations annually. This is an estimated 1–2 amputation per minute. Lower limb amputations are the most common, with most being due to vascular disease. 85% of lower limb amputations are preceded by a foot ulcer. About half of the people with diabetes who get a lower limb amputation will receive a second amputation [4]. African American populations are four times more likely to get an amputation than Caucasian [5]. Around a third of these patients have persistent depression and anxiety after their amputation [6]. Financially, it is noted that amputees have higher healthcare costs and if the amputation was related to vascular disease higher mortality [7].

All these factors can lead to an unknown fear for a patient undergoing an amputation. Understanding the cause of an amputation first is paramount. This can help guide a plan for better pain control in the perioperative period. The main

causes of amputation are progression of disease processes such as peripheral vascular disease (82%) including ischemia and thrombosis. Diabetes and infections such as osteomyelitis and gangrene that is unresponsive to antibiotic treatment. The second major cause is trauma (16.4%). This has a high predominance in upper extremity amputations. Lower extremity amputations with trauma can also be seen with severe fractures that do not heal and frost bites as other causes. Finally, surgical removal of malignancies (0.9%) can result in amputations in upper or lower extremities depending on the location and type of the tumor and growth. Congenital malformations (0.8%) make up the final list for amputation categories [1, 2].

It is important as we consider the cause of the amputation and perioperative pain control, we also factor in the amount of time each patient had before surgery for their amputation decision. A diabetic patient that had a long time to make a decision for an amputation may have had considerable time to go through the stages of grief and accept the amputation as opposed to a trauma that did not have this time. Other things to consider are support system that the patient has at home. As discussed, wound healing is brief, but psychological healing will take longer in most and require repeated support and reminders to the patient to keep moving in a positive direction [8]. In addition to medical management, these patients will need pain-coping strategies and too many these may be a new technique for them in a life altering situation.

2. Pain classification with an emphasis on amputees

Amputation patients have a variety of different pain to consider when treating them in the perioperative setting. The broad classification of this pain is post-amputation pain. However, further classifying it in four categories helps to better understand each pain and how it originates. They are acute post-operative pain, phantom sensations, residual limb pain and phantom limb pain [2, 3].

Acute post-operative pain is the pain that most surgical patients experience after any surgery. It is the pain at the surgical incision site related to surgical trauma, swelling and tissue damage. This is usually reported as sharp and stabbing by patients due to nociceptive afferent nerve supply at the surgical site. Patient can also report muscle spasms related to the immobility of the limb or the compression dressing or brace applies to the amputation site after surgery [2, 9, 10].

Phantom sensations are the non-painful sensations arising from the amputated extremity. This is reported by 75% of patients 4 days after the amputations and higher at 6 months. This can be perceived as movement of the prior extremity or portion of the extremity (i.e. toe or finger). The patient can also note temperature changes or position changes or the missing limb. This has also been noted in mastectomies, dental extractions, and enucleations as well, and can also be seen in spinal cord injuries. Many of the phantom sensations are mild and decline but some patients have some degree persistent sensations indefinitely. There are a few patients in whom these sensations progress to severe pain and become problematic, leading to residual limb pain or phantom limb pain. There are reports of phantom sensations that do fade away and they appear to do this in a progressive fashion called telescoping. This is most common in upper extremity amputations where the phantom sensations continue to decrease such that eventually the patient is left with a sensation of the hand on the stump alone instead of distal [2].

Residual limb pain (stump pain) is the pain localized to the remained affected body segment and can be present for years. Residual limb pain can be of many

different modalities as it can be described as deep tissue pain, superficial incision pain and neuropathic in nature. 75% of patients will experience a component of this chronically after surgery [11]. Neuropathic pain will be described as burning and electric in nature. Some patient may even become hyperalgesia or have allodynia on the stump site. This may lead to difficulty with prosthetic fitting for the patient. This pain is usually noted early in recovery. There are causes of increased stump pain: infection, stump neuroma, heterotopic ossification [9]. These should be assessed with prolonged or increased stump pain as these are easily treatable. Infection is not uncommon in these patients due to high prevalence of diabetes and peripheral vascular disease. This should be assessed and treated with antibiotics accordingly to prevent sepsis and wound dehiscence. Stump neuromas occur when the severed nerve at the amputation site have an inflammatory mediated immune reaction. This can cause pain, but it can also cause unmyelinated A and C fibers to form around the nerve. Neuromas develop over time and usually are characterized by point pain on the stump and sensory changes. Heterotopic ossifications usually occur later after amputation as well. These are calcium deposits that occur in the soft tissue of the stump. These ossifications occur much higher in traumatic amputations. There is some association with traumatic brain injury and the risk of this occurrence as well [2, 3, 12].

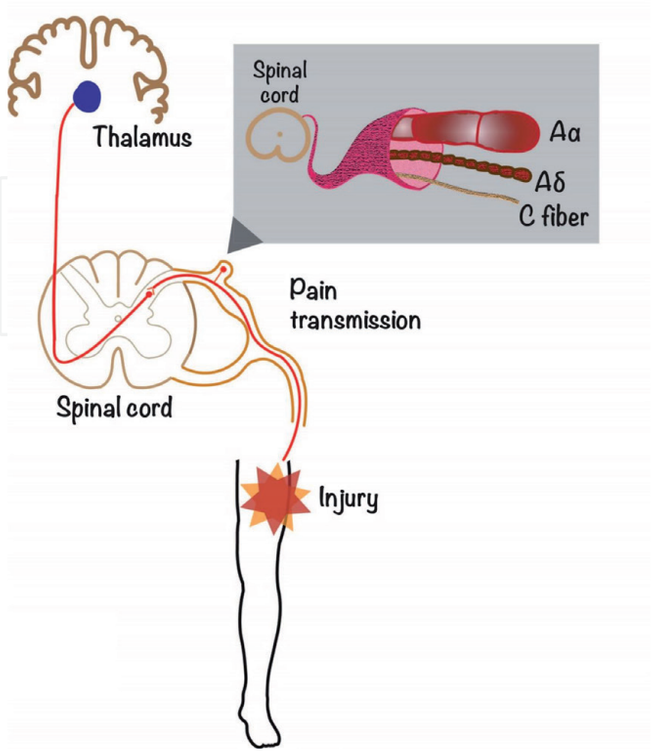
Phantom limb pain was first described in 1462 by French Surgeon, Ambrose Pare' [13]. However, it was not until 1871 that Silas Weir Mitchell, a Civil War surgeon, called this phenomenon "phantom limb" [2, 13]. Phantom limb pain is an unpleasant or painful feeling in the amputated extremity. 45–85% of patients from amputations can suffer from phantom limb pain [9]. This can have neuropathic components with burning and electrical shooting pain and nociceptive components of dull, aching, crushing and cramping pain [13]. There are two times of onset for this pain. One is usually early after amputation in the first month and the second can occur a year after amputation. The further out a patient is from amputation the less likely they will experience this. However, if a patient does begin to experience this, it can last for years. Phantom limb pain does not always have to occur alone and usually occurs with residual limb pain. While residual limb pain may be bothersome early on, phantom limb pain persists and become more bothersome later and tends to last longer. Risk factors for development or prolonging phantom limb pain are found in **Table 1** [1–3, 12, 13].

1. Female gender
2. Elevated pre-amputation pain
3. Upper extremity
4. Increasing age
5. Bilateral amputation
6. Traumatic amputation
7. Stump healing
8. Disease states such as fibromyalgia, migraines, Raynaud's, IBS, irritable bladder, depression, and anxiety
9. Poor social support
10. High expectations
11. Poor coping strategies

Table 1.
Risk factors for developing or prolonged phantom limb pain.

3. Pain signal transmission

To understand how to treat the pain from amputations, we should first take a moment to review how painful stimulation is transmitted through the body (see **Figure 1**). The human body receives signals from various inputs. If something painful happens to the body such as surgical insult, the damage is registered by nociceptors in the periphery. The distal nerve fibers coalesce and become peripheral nerves. There are pain receptors that present on the neuron and it is connected by an axon to the spinal cord. Transmission from peripheral nerve to dorsal column is obtained by different nerve fibers. These include: A-alpha fibers, the A-beta fibers, the A-delta fibers, and the C fibers. Pain travels on two different nerve fibers: A-delta and C-fibers. A-delta fibers are large myelinated fibers that carry sharp pain, whereas C-fibers are small and unmyelinated fibers that produce dull, slow spreading pain. This signal arrives to the dorsal horn and then travels up via neurotransmitters to the brain. There are a variety of neurotransmitters from the spinal cord to the thalamus. For pain, the most important to consider are Substance P which is an excitatory neurotransmitter for second order neurons in the dorsal horn. This neurotransmitter has been shown to sensitize nociceptors. In addition to pain, Substance P also related to inflammation, cell growth, vasodilation and even mood regulation. Glutamate is also a primary neurotransmitter for pain. It is the main excitatory neurotransmitter in the body. In the brain, glutamate receptors can be both pro-nociceptive as well as anti-nociceptive. This leads to many pain therapies constructed at glutamate. This is used for central sensitization in chronic pain patients [14]. Once in the dorsal horn, the second order neurons connect with thalamus and other various areas. These can include the somatosensory cortex (physical sensation), limbic system (emotion) and frontal cortex (upper level thinking). This allows a patient to feel and react with pain not just physically but emotionally as well [15].



Pain Neurotransmitters

Excitatory	Inhibitory
Substance P	GABA
Glutamate	Glycine
Calcitonin Gene Related Peptide	Adenosine
ATP	Serotonin
Aspartate	Norepinephrine
	Somatostatin
	Enkephalin

Figure 1.
Path pathways.

Let us revisit how the various pain pathways are affected during amputation. Phantom pain sensations likely result from changes in the somatosensory cortex. This causes afferent nociceptive stimulation from body parts near the amputation sites (such as face for upper extremity amputation or bladder for lower extremity amputation). Due to this reorganization in the somatosensory cortex and stimulation input, the phantom sensations occur [2, 9].

Peripheral nerves likely play a large role in the phantom limb pain and residual limb pain. Damage to distal nerve endings and axons causes inflammation and alteration in neurotransmission along the usual pain pathway. The distal nerve endings will begin to regenerate but there will be non-functional axons, changes in sodium and potassium channels and different input from the spinal cord. Neuromas can form here as discussed previously. This can also result in higher pain due to more catecholamines in circulation due to increased sympathetic discharge [2, 9].

There are also spinal cord changes in the dorsal horn related to pain after amputation. The peripheral nerves are no longer able to send the usual signals along the axons to the spinal cord. The brainstem reticular areas therefore do not send inhibitory sensory transmission, so the dorsal horn receives input from this body part as high sensory feedback resulting in pain transmission [1, 2, 9].

These changes in the peripheral and spinal cord need to be considered as we are thinking about treating each patient for amputation pain.

4. Protocol for perioperative caring for amputation patients

It is well understood that effective control of acute post-amputation pain results in decreased risk of development of residual and phantom limb pain [16]. Perioperative plans need to set up within a multi-disciplinary team, ideally involving surgeon, anesthesia, in-patient acute pain teams, pharmacy, physical therapy, occupational therapy, nutrition, and social work to name a few. The pre-operative optimization is essential to control of acute post-amputation pain and help decrease the risk of development of chronic and phantom pain to help these amputation patients have the best chance for better pain control post-amputation. Thorough pre-operative evaluation is needed to look at co-medical conditions that can be optimized. The patient's nutrition should be optimized for wound healing as well. Physical therapy and occupational therapy should work with the patient before surgery to improve physical status prior to surgery and make post-operative recovery more successful. Patient should have a pre-operative discussion about post-operative pain management and expectations. This will allow goal setting and help with anxiety the patient may be experiencing.

Patients who struggle with high pain scores prior to amputation may have an elevated risk of developing chronic pain [17]. Thus, aggressive multimodal analgesic therapy instituted pre-operatively and early in the post-operative period could be beneficial in reducing the incidence of chronic pain. One study found that the presence of depressive symptoms was also a predictor of increased intensity of chronic pain in amputees [18]. Thus, it may be worthwhile to address these symptoms prior to elective amputation surgery. Patients with a complex history of chronic pain disorders and/or patients having high baseline daily opioid requirements (> 80 mg oral morphine equivalents) should be further selected to undergo a pre-operative appointment with a pain specialist. This appointment should ideally take place around 4 weeks prior to elective amputation with the goal to optimize the patient's pain regimen pre-operatively, by maximizing non-opioid modalities and reduction of daily opioid consumption if possible. This is done to improve response

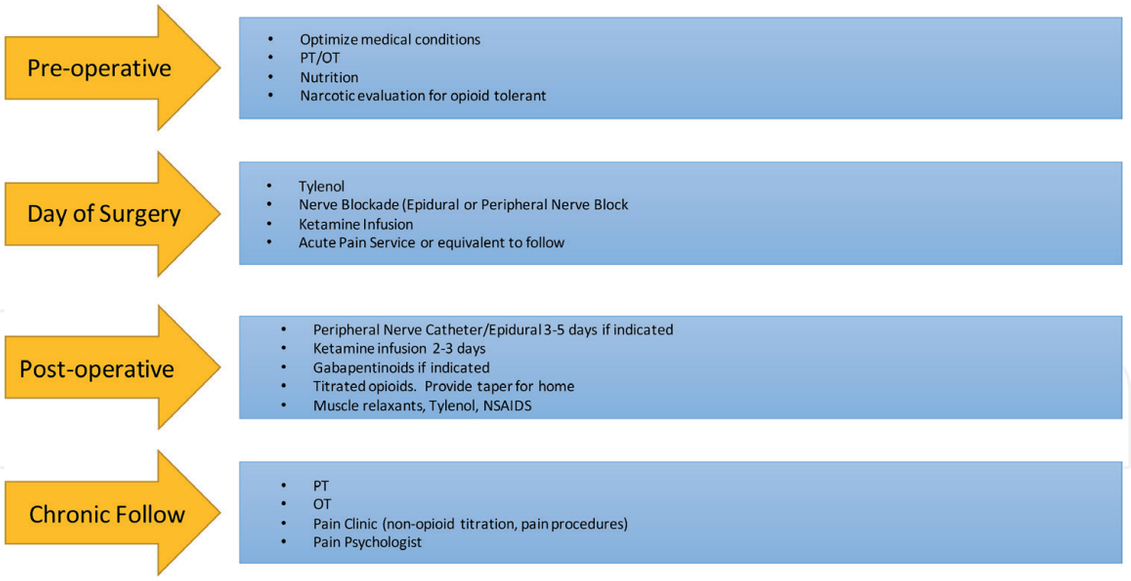


Figure 2.
Protocol for amputation pain management.

to opioid therapy in the immediate post-operative period. Thorough patient education and compassionate counseling also play a key role in developing a team relationship with the patient [19, 20]. See **Figure 2** for full protocol.

5. Nerve blockade

The current standard of care is pre-operative nerve blockade to prevent peripheral sensitization leading to future onset of phantom limb pain. Successful outcomes necessitate effective communication between the surgeon, anesthesiologist, and the various teams involved in the post-operative rehabilitation of the patient. A consultation with the Acute Pain Service or similar entity that performs peripheral nerve blockade pre-operatively and then follows the patient during their post-operative inpatient course is an important factor in the success in early prevention of acute and chronic pain for these patients.

Most patients that arrive for amputations should be evaluated to receive pre-operative peripheral nerve blocks. If this cannot be done pre-operatively, patients can be evaluated post-operatively for a nerve block. If patients do not require post-operative anti-coagulation that will preclude a continuous peripheral nerve catheter, this would be the preferred nerve block for these patients as this will help with prevention phantom limb pain and chronic post-operative pain [3]. This can be utilized for 3–5 days. Continuous nerve catheter infusions have been found to decrease post-operative morphine requirements [21]. However, in addition, there are other factors that may preclude continuous peripheral nerve catheter placement such as infection, and patient factors. If this is the case, single shot peripheral nerve blocks may be utilized. Interestingly, a systematic review and meta-analysis found no difference in pain scores at 24 hours between patients that received a nerve block and those that did not [22]. However, this study did not look at chronic pain in these patients which is the important component that these nerve blocks are used for [9].

It is important to understand the anatomy of the amputation site to have successful nerve block placement. For example, a below the knee amputation will rely heavily on a sciatic nerve blockade whereas an above the knee amputation will need blockade of both femoral and sciatic nerves for successful pain control and help with peripheral sensitization for the patient [9]. For upper extremity amputations, a forearm

amputation will be lower in the brachial plexus than an above the elbow amputation or shoulder disarticulation. Tourniquet site is also paramount when planning peripheral nerve block placement. If the catheter is in the surgical site or tourniquet site, there is a risk for dislodgement. It is important to remember this with placement and keep the securement of catheter out of the surgical field. This will take good communication between anesthesia provider and surgeon to achieve this effectively.

It should be noted that epidural blockade may also be used for lower extremity amputation, especially if it will be a bilateral lower extremity amputation. There are studies that show pre-operative epidural placement in amputation patients prevent phantom limb pain due to stopping nociceptive input to the spinal cord [3]. There is no comparison of epidural to peripheral nerve catheters for lower extremity amputations, but on a practically note, peripheral nerve blockade will allow better mobilization and participation in physical therapy [3]. In addition, peripheral nerve block does not have the hemodynamic affects that epidural blockade can have [23].

6. Pharmacology

6.1 Opioids

Opioids remain a favored therapy for pain after surgery. They bind to Mu receptors in peripheral and central nerves as an agonist fashion to produce analgesia. They also can affect phantom limb pain by reducing cortical reorganization [10]. There is a wide variety to choose from post-operatively as they come in intravenous and oral formulation. Usually initially a parenteral opioid therapy with a patient-controlled analgesia (PCA) is started on post-operative day (POD) zero. Once the patient is tolerating a diet, the PCA is weaned down incrementally and oral opioid therapy is instituted. For opioid tolerant patients, we attempt to calculate their total daily morphine equivalent requirement and base our starting oral dose based on that. The goal is to wean off the PCA completely by 48 hours, coinciding with the discontinuation of other intravenous infusion [10].

6.2 N-Methyl-D-Aspartate (NMDA) Receptor Antagonists

Ketamine has been studied for post-operative pain. It has been shown that the use of this medication lowers the opioid requirements and reverses opioid tolerance needed for acute post-operative pain [24]. Ketamine is a noncompetitive NMDA receptor antagonist that targets primarily in the brain and spinal cord. The NMDA receptor is important for synaptic plasticity, central sensitization, amplification of pain signals and opioid tolerance. For amputations, it lowers the dorsal horn sensitization and stops the events that may lead to phantom limb pain and residual limb pain. Important to note, it will not prevent phantom limb pain but will reduce risks of phantom limb pain and residual limb pain [9]. Ketamine has also been shown to have anti-inflammatory properties which may be effective in the early pre-operative phase. Ketamine infusions can be started in the operating room and continued for 2–3 days post-operatively. Studies show low does ketamine infusions do reduce opioids immediately post-op but there was not a significant reduction in immediate post op pain ratings [2, 3, 10].

6.3 Gabapentinoids

Gabapentin and pregabalin are both anti-convulsant that inhibit alpha 2-delta subunit of voltage-gated calcium channels. They are structural like GABA

neurotransmitter, but they are unable to bind to any GABA receptors. In addition to the use with seizures, it has been used for chronic pain, especially neuropathic in nature. Dosages must be titrated slowly, and results are not seen immediately. These doses also must be adjusted for patients with impaired renal function with the help of a pharmacist [25, 26]. However, some studies claim that its efficacy to treat phantom limb pain is inconclusive and limited by dose dependent side effects like somnolence and dizziness [2]. There are other studies more recently that show promise of administration of gabapentinoids for reducing chronic post-surgical pain and this can be exploited to amputees as well [3, 9, 10].

6.4 Acetaminophen

Acetaminophen's exact mechanism of action is not well understood, but it is thought to reduce the production of prostaglandins in the brain. Prostaglandins are chemicals that cause inflammation and swelling. Acetaminophen relieves pain by elevating the pain threshold, that is, by requiring a greater amount of pain to develop before a person feels it. Acetaminophen administration to amputation patients will help with inflammation and an adjunct to help with post-surgical nociceptive pain, which has been shown to decrease opioid requirements. Acetaminophen dosages will be lowered in patients with pre-existing liver disease [27]. This will be the most beneficial in the early pre-operative phase. It may be especially beneficially to start prior to the amputation as part of a pre-emptive analgesia. This is thought to protect the central nervous system from noxious insults which result in the patient getting hyperalgesia and allodynia [10, 28].

6.5 NSAIDs

NSAIDs work by inhibiting the activity of cyclooxygenase enzymes (COX-1 or COX-2). By blocking the Cox enzymes, many prostaglandins are not made. This means that there is less swelling and less pain. Most NSAIDs block both Cox-1 and Cox-2 enzymes. For pain, this specifically looks at enzymes that work with prostaglandins for inflammation. Like acetaminophen, these medications work well in the acute perioperative phase for nociceptive pain and reducing opioid requirements. Their use can be limited due to post-operative bleeding concerns. Usually these medications do not help with chronic post amputation pain or phantom limb pain. A short course may be suitable for some patients that have normal renal function; however, we do not advocate for chronic NSAID therapy due to the risks of gastrointestinal bleeding and renal toxicity [10, 23, 29].

6.6 Muscle relaxants

As discussed earlier, acute post-operative pain can have spasmodic pain proximal to the stump site, likely due to tissue inflammation. This can also be present with residual limb pain in some patients. There are a variety of muscle relaxants that can be tried for a short period of time [30]. If the patient is on opioids, would be cautious of adding a benzodiazepine for muscle relaxant. There is a lack of adequate literature supporting the use of muscle relaxants for post amputation pain.

6.7 Tri-cyclic antidepressants and selective norepinephrine reuptake inhibitors

Anti-depressants are commonly prescribed for chronic neuropathic pain and coexisting depression that accompanies it. These medications work by inhibiting serotonin-epinephrine uptake blockade, NMDA receptor antagonism and sodium

channel blockade. These medications have not been shown to work effectively in phantom limb pain in studies. These are not usually done in the perioperative setting as they require careful titration over weeks to months which is better done as outpatient therapy. Side effects of opioids and other modalities may warrant a small dose trial in the perioperative setting to help with uncontrolled acute or phantom limb pain [9, 10, 31].

6.8 Calcitonin

Calcitonin is a hormone secreted by thyroid gland in parafollicular cells. Unlike the parathyroid hormone, its job is to reduce calcium in the blood. There are synthetic forms of this used for chronic pain syndromes. The exact pain mechanism of action is unknown. There are mixed results of phantom limb pain [10]. The greatest benefit has been shown when it is administered early in the perioperative period; usually within the first 7 days [32]. There are reports of complete resolution of phantom limb pain with its use [9].

7. Therapeutic modalities

There are many additional modalities that may be of benefit to amputee patients after the initial perioperative period to help with phantom limb pain and residual limb pain. Many of these involve experienced providers and therapists [2, 10, 12, 33–36]. These are summarized in **Table 2**.

1. Desensitization techniques
2. Mirror therapy
3. Massage
4. TENs
5. Exercise
6. Hot/cold therapy
7. Biofeedback
8. Peripheral nerve stimulation
9. Prolonged peripheral nerve blockade
10. Sympathetic nerve blocks
11. Deep brain stimulators
12. Spinal cord stimulators
13. Neurolysis

Table 2.
Therapeutic modalities for chronic amputee limb pain.

8. Conclusions

As patient's present for amputations, it is important to remember the care for these patients needs to be multi-disciplinary to prevent chronic pain. If perioperative pain plans are developed early and worked on as a team, the patient will benefit the most and have the best chance for success at not having long-term phantom limb pain and/or residual limb pain which adversely impact their quality of life.

Psychological preparation is paramount but may not always be accomplished if amputation is needed in emergent or traumatic fashion. These patients can still be cared for effectively in a modified format with high success rate if early post-operative intervention is achieved.

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