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SPECIAL TOPIC
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The Peripheral Nerve Surgeon's Role in the Management of Neuropathic Pain

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Summary: Neuropathic pain (NP) underlies significant morbidity and disability worldwide. Although pharmacologic and functional therapies attempt to address this issue, they remain incompletely effective for many patients. Peripheral nerve surgeons have a range of techniques for intervening on NP. The aim of this review is to enable practitioners to identify patients with NP who might benefit from surgical intervention. The workup for NP includes patient history and specific physical examination maneuvers, as well as imaging and diagnostic nerve blocks. Once diagnosed, there is a range of options surgeons can utilize based on specific causes of NP. These techniques include nerve decompression, nerve reconstruction, nerve ablative techniques, and implantable nerve-modulating devices. In addition, there is an emerging role for preoperative involvement of peripheral nerve surgeons for cases known to carry a high risk of inducing postoperative NP. Lastly, we describe the ongoing work that will enable surgeons to expand their armamentarium to better serve patients with NP. *(Plast Reconstr Surg Glob Open 2023; 11:e5005; doi: 10.1097/GOX.0000000000005005; Published online 19 May 2023.)*

INTRODUCTION

Neuropathic pain (NP) can be a devastating problem. Many patients spend years in search of relief. NP is defined as "pain caused by a lesion or disease of the somatosensory system."[1,2] Patients typically describe burning, electric shocks, shooting pain, and pain from light touch, warmth, or cold.[3] It is estimated to affect 27–33 million Americans[4–6] and impairs quality of life.[7] NP is also costly to the healthcare system; NP following surgery or trauma costs over $40,000 per patient per year.[8] Thus, NP is a challenging problem for patients, clinicians, and the healthcare system.

The causes of NP are manifold. NP begins with the somatosensory fibers that sense pain, which undergo insults from medical disease, trauma, or surgery. These high-threshold sensory neurons transmit signals to the nociceptive pathway of the spinal cord and brain, alerting the individual to perception of injury. NP is fundamentally a dysfunction of this circuit, in which it becomes hyperactive.[9] The causes of NP can be broadly divided into lesions of the central[10] or peripheral nervous system.[11] Recently, a four-part taxonomy of peripheral nerve pain has been described: compression neuropathy, neuroma, painful hyperalgesia, and phantom nerve pain.[12] These four domains encompass the major causes of NP (Fig. 1). The goal of this article is to provide an overview of the tools available for the peripheral nerve surgeon for diagnosis, treatment, and prevention of NP.

Nerve compression is a well-known cause of NP.[13,14] Many anatomical sites are prone to nerve compression, including the carpal tunnel, cubital tunnel, common peroneal nerve, and vertebral foramina.[15] Chronic nerve compression creates a proinflammatory state in the perineural environment, resulting in increased cytokine and lymphocytic infiltration.[16–18] This physical and paracrine engagement between somatosensory neurons and their neighbors is a key driver of NP.

Direct nerve injury is another major cause of NP. Transected axons undergo Wallerian degeneration distally,[19] and the proximal neuron ultimately forms a neuroma.[20] Neuromas are bundles of disorganized axonal fibers formed during failed attempts at regeneration and distal reconnection.[21] It is a staged process of damage, degeneration, sprouting, and unorganized growth that drives inappropriate activation of the nociceptive pathway.[22] Every time a nerve is transected, a neuroma forms. However, not all neuromas result in symptomatic pain for patients.[22] The drivers of this differential outcome are still

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under investigation. Certain anatomical sites seem to be at greater risk; a recent review of over 600 neuromas identified the extremities as the major site of painful neuromas.[23] The mechanism of injury also correlates with risk of neuroma formation, with traumatic amputation elevating risk of symptomatic neuromas in both digital and upper extremity injury patients.[24,25] In addition, a review of lower extremity amputees found that a more proximal injury site increased the incidence of painful neuroma formation.[26] Further research will likely identify and clarify risk factors.

Finally, disruptions at the circuit level contribute to NP. Changes in the areas of central processing of pain can drive NP.[27] Experimental research in rats has shown that shifts in the interactions of different thalamic neuronal subsets contribute to hyperalgesia.[28] Functional brain imaging has shown alterations in the strength of input from the anterior insular cortex in patients with hyperalgesia.[29] A key example of circuit disturbance is phantom limb pain, in which amputees experience NP mapping to their missing limb. Loss of sensory input from the amputated part induces disequilibrium in the somatosensory circuit, manifesting as phantom pain.[30,31] In addition, phantom pain is often accompanied by a symptomatic neuroma, theorized to induce circuit disequilibrium via atypical input from the neuroma.[32] Thus, from the cerebral cortex to the sensory nerve endings, imbalance in the nociceptive pathway contributes to NP.

DIAGNOSIS AND PATIENT SELECTION FOR SURGICAL INTERVENTION

Surgeons will invariably treat patients experiencing NP, typically following surgery or trauma. As such, the ability to effectively diagnose NP is critical. However, not all patients with NP will benefit from operative intervention. Identification of appropriate surgical candidates is therefore a major focus.

Diagnostic workup of NP includes a detailed history and specific physical examination maneuvers. First, NP must be differentiated from other forms of chronic pain. Electric shocks, hypersensitivity, allodynia, paresthesias, numbness, and shooting pain in the region of a known nerve distribution are emblematic of NP. Such pains experienced in a missing body part are specific for phantom pain. Patient questionnaires have been developed to identify NP,[33] including Douleur Neuropathique 4[34,35]; Neuropathic Pain Symptom Inventory[36]; and Leeds Assessment of Neuropathic Symptoms and Signs, which predicts NP risk following thoracic surgery.[37] These questionnaires can be incorporated into clinical workflows.

Surgical history is also important in diagnosing NP. Certain procedures carry a higher risk of postoperative symptomatic neuroma formation and painful hyperalgesia. One systematic review analyzing postsurgical NP found that thoracic procedures carried the highest risk (68%), groin hernia repair had an intermediate risk (31%), and knee arthroscopy had a low risk (6%).[38] Breast surgery patients have a 20%–40% risk of chronic postoperative pain.[39] Amputation procedures are particularly well known for their risk of NP. Rates in upper extremity amputations have been reported from 25% to 42%.[24,40] In lower limb amputations, one

Takeaways

Question: How can surgeons diagnose and treat patients with neuropathic pain?

Findings: Neuropathic pain can be a significant problem following surgery or injury. Diagnosis is made with a careful history and examination of the patient, as well as selective imaging and diagnostic nerve blocks. Surgeons can offer procedures aimed at reducing neuropathic pain. Innovative solutions are being developed to improve treatment of neuropathic pain and work towards prevention.

Meaning: Peripheral nerve surgeons, working with many specialists, have much to offer patients with neuropathic pain.

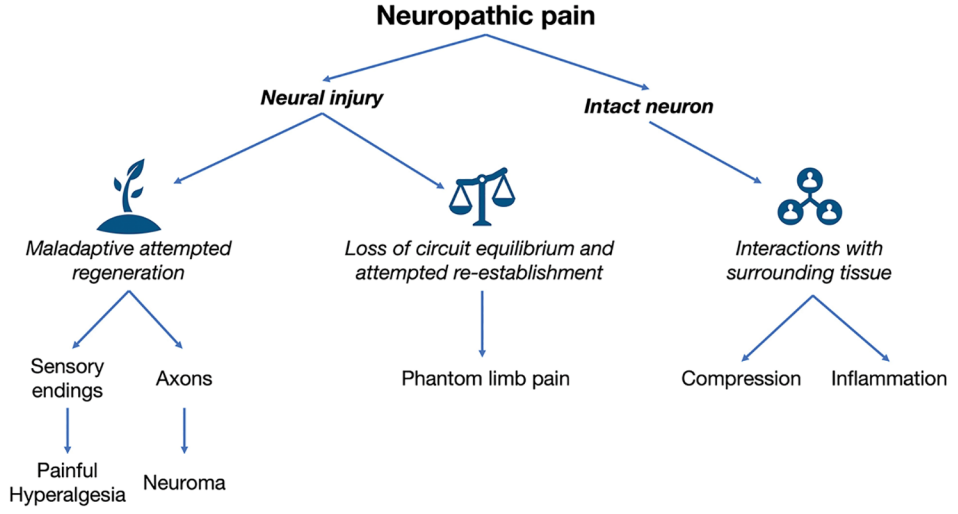

Fig. 1. Key mechanisms underlying neuropathic pain.

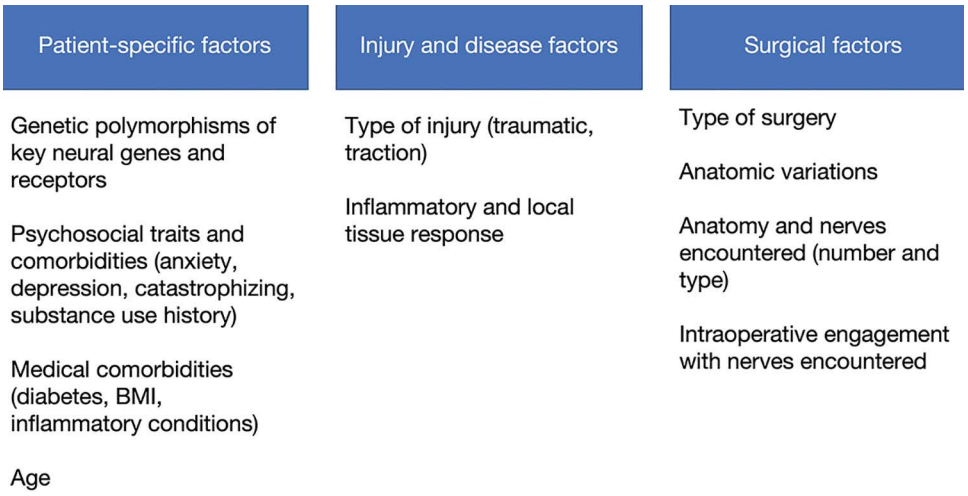

Fig. 2. Preoperative risk factors of postoperative pain.

single institution report revealed a rate of symptomatic neuroma formation of 4%,[41] while other studies have indicated the rate of all cause NP is as high as 74%.[42] Given the prevalence of postsurgical NP, there should be a high clinical suspicion for NP in patients who have undergone the above procedures who present with pain. Because these patients have likely undergone direct nerve injury, they should be referred to a peripheral nerve surgeon. Patient specific factors such as psychosocial status and health have also been correlated to rates of postoperative NP. A recent meta-analysis highlights that anxiety, depression, and catastrophizing are significantly associated with postoperative pain.[43] Substance use history has also emerged as a predictor of postoperative NP.[44] Other comorbidities have been linked to increased rates of NP including diabetes and elevated BMI.[45] Thus, history of certain operations and psychosocial comorbidities should increase clinical suspicion for NP (Fig. 2).

Along with patient's history, a detailed physical examination is paramount in diagnosing NP. Knowledge of peripheral anatomy allows the surgeon to directly test the function of the nerve in question. If the patient's pain does not map to a known course of a nerve, then the likelihood of NP is low. Sensory testing includes light touch, vibration, proprioception, two-point discrimination and cold/heat tolerance. Motor testing includes a full assessment of the muscles innervated by the suspected nerve and neighboring muscles. Finally, the Tinel test is often positive in patients with neuromas and can be helpful in pinpointing a compressed or hyperalgesic cutaneous nerve.[46]

Diagnostic blocks are a powerful tool in assessing NP. They can confirm that pain in a specific nerve distribution is in fact driven by the suspected peripheral nerve. For example, if a patient's pain correlates to the common peroneal nerve, and successful nerve block is a strong indication that the nerve is compressed or formed a neuroma; several recent studies have highlighted the positive predictive value of blocks.[47,48] Additionally, blocks demonstrate that peripheral intervention can improve clinical phenotype, justifying the decision to pursue surgery.[49,50] Because of these capabilities, in addition to relieving pain, diagnostic blocks are frequently utilized in our patients. Lastly, the role of imaging in the diagnosis of NP varies by etiology. In cases such as spine compression[51] and inflammatory causes,[52,53] MRI has proven valuable. MRI can also reliably identify larger

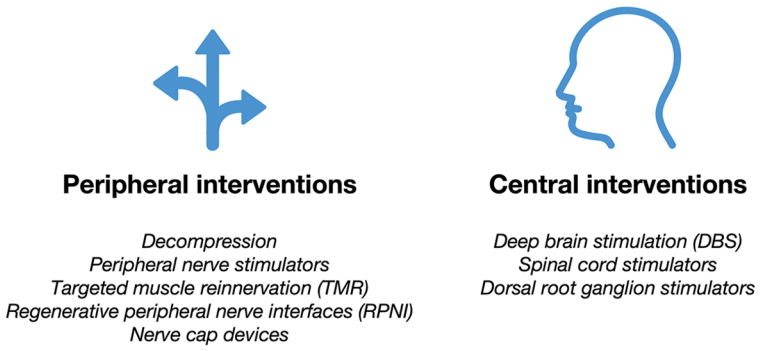

Fig. 3. Surgical options for neuropathic pain organized by location of intervention.

neuromas in lower limb amputees[54] and provide important information about the location and pathology of peripheral nerve lesions.[55] High resolution ultrasound (US) continues to demonstrate utility in the assessment of extremity nerve entrapment[56] and localizing neuromas.[49,57] A set of diagnostic criteria —including patient's history, physical exam, imaging, and response to diagnostic block—has been described in the literature.[49] In brief, a patient must have pain and symptoms in a defined neural anatomic distribution or history of nerve injury or suspected nerve injury. They must also have one of the three examination findings: positive Tinel sign, positive response to a diagnostic local injection, or imaging via ultrasound or MRI confirming neuroma.[48]

Once NP is diagnosed, there are many therapies available to treat the patient's pain. Discussion of nonsurgical options is beyond the scope of this review. Briefly, they include a number of medications, such as gabapentin, antidepressants, tramadol, opioids, and cannabinoids.[58,59] Psychotherapy techniques are also used.[60] In addition, a number of nonsurgical interventions can be attempted, such as radiofrequency ablation,[61] Botox injections,[62] central stimulation,[63] and peripheral stimulation (including transcutaneous electrical stimulation).[64] Each of these techniques has shown promise, but no single modality has been shown to be universally successful. Therefore, a patient with NP and clinical suspicion for nerve injury, compression, or neuroma whose nonsurgical therapies have failed should be evaluated by a peripheral nerve surgeon.

SURGICAL TREATMENT OPTIONS FOR NEUROPATHIC PAIN

The surgical options for NP are many and must be tailored to the underlying disease etiology (Fig. 3). In compression neuropathy, decompression surgery may offer relief. Common sites of nerve compression include the carpal tunnel, Guyon's canal, cubital tunnel, thoracic outlet, vertebral foramina, tarsal tunnel, common peroneal nerve at the fibular head, and many others.[15] Recently, these techniques have been expanded to include headache surgery.[65,66] Overall, the surgical techniques for nerve decompression are a well-established mechanism by which nerve surgeons help patients with compression-induced pain.

Symptomatic neuroma management includes a range of surgical techniques aimed at removal of the neuroma and prevention of recurrence.[67] In the 1980s, neuromas were excised and free nerve ends were implanted into surrounding muscle fibers; a reduction in pain was reported in over 80% of patients.[68] This technique, however, appears to have high recurrence[69] and re-operation rates.[23] Techniques like targeted muscle reinnervation (TMR) and regenerative peripheral nerve interfaces (RPNI) have been shown to limit neuroma formation by giving the regenerative bud of damaged axons a new target for innervation.[67] TMR involves coaptating the transected sensory or mixed nerve into a nearby motor nerve branch. Originally developed to improve myoelectric prosthesis control,[70] reports of improvement in pain among these patients led to repurposing of TMR for treatment and prevention of NP.[71] TMR has been shown to improve residual limb pain in a randomized control trial of amputee patients. These patients also reported reduction in phantom limb pain.[72] Similarly, RPNI involves transposing free nerve ends into free autologous muscle grafts. Evidence in amputee patients has shown that RPNI can treat symptomatic neuromas.[73] The last decade has seen a marked expansion in utilization of TMR and RPNI. TMR has expanded to other surgeries, including breast,[74] abdominal wall,[75] and headache surgery.[76] Likewise, studies have shown RPNI can treat symptomatic neuromas in amputee patients.[73] RPNI has also grown to include headache[76] and breast surgery.[77] Innovation in TMR and RPNI is likely to continue to expand the role of both techniques across injury sites.

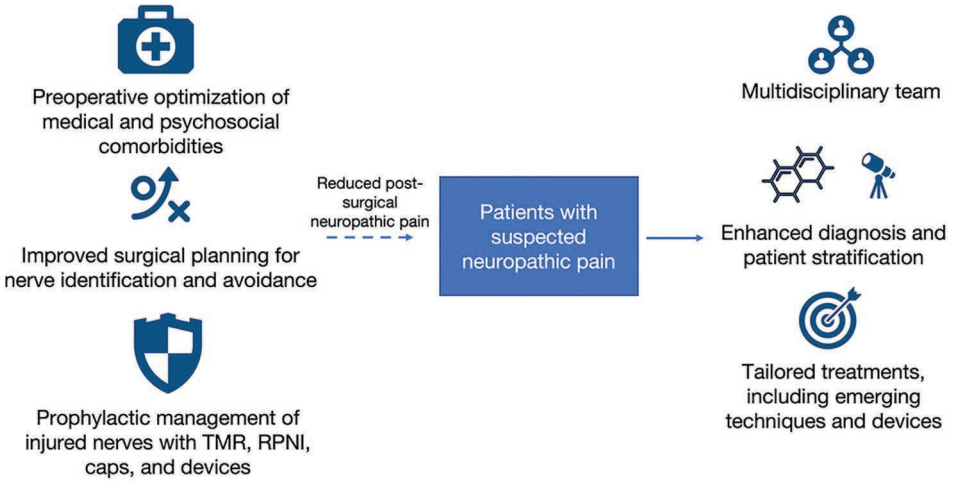

Fig. 4. Future direction for surgical management of neuropathic pain.

For NP driven by circuit disequilibrium seen in phantom pain or complex regional pain syndrome, a range of surgically placed devices can be used. They often rely on electrical stimulation to modulate the somatosensory pathway. Centrally, deep brain stimulator devices have been implanted for NP,[78] with durable pain reduction following amputation and brachial plexus avulsion,[79] including in patients with NP refractory to pharmacotherapy.[80] A meta-analysis found that deep brain stimulator improves quality of life in NP patients.[81] In the spinal cord, stimulators have also been used to control NP via stimulation of the dorsal columns. Spinal cord stimulators have been found effective in a randomized control trial for NP after failed back surgery syndrome[82] and limb pain.[83] Stimulators have also been placed on the dorsal root ganglion, showing high patient satisfaction[84] with durable pain reduction at both 1 year[85] and 3 years in patients with upper and lower limb NP.[86] Finally, peripheral nerves stimulators, placed under ultrasound, have been shown in a double-blind randomized control trial of lower limb amputees with NP to significantly reduce pain compared with placebo.[87] These percutaneous devices remain a critical research area,[88] given potential for minimally invasive use. Furthermore, additional recent research hypotheses have pointed to the important role that injury to the peripheral nerve can have on upregulating central nervous system pathways towards centralization of NP. By preemptively addressing such peripheral nerve pathology via nerve surgery techniques, coupled with improvements in multi-modal therapy and treatment regimens, practitioners may not only reduce or prevent centralization of NP but may also reduce opioid use and dependence for those with under- or untreated peripheral nerve injuries.

MOVING TOWARD PREVENTION OF NEUROPATHIC PAIN

Given the high rates of NP after surgery, focus has shifted toward prevention. Preoperative patient optimization is critical. Control of medical comorbidities, including psychological optimization, is likely to reduce a patient's presurgical risk of NP (and other complications). Likewise, engagement with psychosocial supports to optimize patients before surgery may limit NP, as shown in a large meta-analysis of breast cancer patients.[89] These interventions may reduce a patient's a priori risk of NP.

Intraoperatively, prevention of NP is based on identification and avoidance of nerve injury. Knowledge of nerve anatomy, including the smaller branches of major nerves, minimizes the risk of injury and subsequent NP. Additionally, many patients exhibit variable nerve courses. Surgical case series and cadaveric studies have revealed a range of anatomic aberrations of the median nerve,[90] tibial nerve,[91] ilioinguinal and genitofemoral nerves,[92] and brachial plexus.[93] Awareness of these anomalies can help reduce the likelihood of nerve injury.

If intraoperative iatrogenic nerve injury occurs, early recognition can limit the risk of NP. Depending on the extent of injury, a range of techniques can be used. If the distal end is available, nerve repair or grafting with nerve autografts or allografts can be effective. Autografts are the gold standard for nerve reconstruction but require sacrifice of sensation at the donor site.[94] Allografts may therefore be used preferentially for painful conditions, or in situations in which the primary goal is prevention of NP.[95] These options are effective for reduction of NP following surgical nerve injury. If nerve repair of an injured sensory nerve is not possible, neuroma prevention techniques such as TMR and RPNI can be used. Additionally, peripheral nerve surgeons are available for intraoperative consultation and should be used when there is concern for iatrogenic neuropathic injury.

Finally, collaboration with peripheral nerve surgeons in the preoperative setting may be useful in cases with known high risk of nerve sacrifice, or injury, and subsequent development of NP. Amputation care provides an example of the efficacy of this collaboration. For example, it is now standard in our practice to have established preoperative consultations with peripheral nerve surgeons for TMR and/or RPNI in all patients undergoing upper or lower extremity amputations. These techniques have shown benefit as prophylaxis against neuromas and efficacy as a prophylactic intervention, effectively limiting neuroma formation during initial amputation.[96–98] Thus, TMR and RPNI can be utilized in the event of nerve injury as a bulwark against postoperative NP.

FUTURE DIRECTIONS

Given the diverse set of techniques in use for treatment of NP, the next decade is primed for continued optimization. Research and innovation across diagnosis, surgical techniques and devices, and health systems have great potential to positively impact NP patient (Fig. 4).

Diagnosis of NP processes is likely to be enhanced by biological, imaging, and computational improvements. New molecular biomarkers of pain are continually discovered, raising the possibility of laboratory-based assessment of patients' somatosensory circuitry and identification of NP.[99] Given the continued expansion of genetic testing and known genetic risks for pain, preoperative genetic evaluation may predict risk of NP. Imaging research continues to highlight the role of novel neuroimaging in understanding the mechanism of individual pain,[100,101] with possible application to diagnosing of NP. Finally, advances in artificial intelligence and machine learning could play a role in predicting pain, based on preoperative factors and imaging.[102,103] We envision a day when patients undergoing procedures likely to cause NP are evaluated with tests that better define their pain risk, and patients with NP are selectively stratified for targeted treatment.

The coming years are likely to see an expansion in the use of TMR, RPNI, and other forms of nerve rerouting techniques. Interestingly, combinations of these techniques with each other and with other NP therapies have been reported.[104,105] Like improved diagnosis, the expansion of these surgical techniques may enable the generation of personalized therapies, engaging with individual pathophysiology more effectively. In addition to techniques,

surgical devices are poised to take on a greater role in the management of NP. Stimulators are already benefiting from improvements in material sciences and bioelectronics.[106,107] Another exciting area is the use of devices that tame postinjury plasticity of nerves or promote effective reinnervation. A number of other synthetic and biological materials are being explored to limit neuroma formation.[108] Implantable devices capable of harnessing this regenerative impulse towards functional nerve restoration remain an exciting area of research. Improvements in biomaterial and nanomaterial sciences are already showing promise in this area.[109,110] In the coming decade, we remain hopeful that these technologies will augment and improve the nerve surgeon's toolkit.

Finally, team-based approaches to NP are likely to continue to expand. NP after surgery exists in the complex medical and psychosocial context of each patient. Therefore, clinicians from the fields of nerve surgery, pain management, physical and occupational therapy, psychology, and social work can contribute to improved care.[111] Harnessing the power of interdisciplinary clinical teams will help empower patients to achieve control over their pain and more fully engage in their lives.

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DISCLOSURES

Dr. Eberlin is a consultant for AxoGen, Checkpoint, and Integra. Dr. Valerio is a consultant for AxoGen, Checkpoint, and Integra. All the other authors have no financial interests to declare in relation to the content of this article.

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