Development of mirror pain following trigeminal nerve injury: a case report and review of neuropathic mechanisms

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Following injury to a peripheral nerve, patients may complain of pain over the distribution of the same contralateral nerve, a phenomenon referred to as *contralateral pain* or *mirror pain* (MP). Symptoms of MP usually begin after the neuropathic pain from the original nerve injury has become chronic. Chronic neuropathic pain can lead to sensitization and spread of pain. Because the diagnosis of MP can be missed, patients may undergo multiple treatment procedures that prove to be ineffective in relieving the pain. This article presents a case of MP that appeared approximately 20 months following inferior alveolar nerve injury that occurred during placement of a dental implant in the region of the first molar. Acutely painful nerve injuries must be aggressively treated to prevent changeover to a chronic pain state characterized by sensitization and spread of pain beyond the initial injury. Consequently, clinicians need to begin effective, early pain management to prevent the changeover to chronic pain that has become centralized and refractive to treatment.

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Following injury to a peripheral nerve, patients may begin to complain of pain over the distribution of the contralateral nerve. This phenomenon is referred to as *contralateral pain* or *mirror pain* (MP). Symptoms of MP usually begin after the neuropathic pain that resulted from the original nerve injury has become chronic. Chronic neuropathic pain can lead to sensitization and spread of pain beyond the area of initial injury. The diagnosis of MP can be missed; as a result, the patient may undergo multiple treatment procedures that prove to be ineffective in relieving the pain.

In an effort to call attention to this clinical problem, this article presents a case of apparent MP that appeared approximately 20 months following inferior alveolar nerve injury (IAN) that occurred during placement of a dental implant in the region of the mandibular first molar. The neural mechanisms responsible for the development and spread of chronic neuropathic pain will be reviewed.

Case report

A 32-year-old woman was referred to the Trigeminal Nerve Injury Clinic at Virginia Commonwealth University, Richmond, for evaluation and treatment of chronic neuropathic pain in her right IAN distribution. The pain had developed after implant placement in the region of the mandibular first molar.

When the patient was first examined at the clinic, it had been approximately 20 months since the injury. The implant had not been removed; it had become fully integrated in bone but was not restored. According to the patient, she experienced loss of sensation without pain immediately after surgery but noted pain beginning 3 weeks after implant placement. She was prescribed narcotic analgesics, told that her symptoms were normal after implant placement, and advised to wait for spontaneous healing that would most likely occur.

After multiple follow-up visits to the implant surgeon over an 8-month period, the patient had experienced no relief in her symptoms. At that time, she independently sought other opinions. No definitive treatment was ever offered by these other healthcare providers, as they recommended that she wait for spontaneous recovery.

At her initial visit to the clinic, she described her pain symptoms as "crawling, rubbery, tingling, electric, itching, and sore." She rated her constant pain at 80% on a 0-100 Likert pain severity scale. She also reported more severe superimposed "electric" pain shocks that were triggered by oral functions and touching of her face. She rated her overall orofacial and neurosensory functional losses as 50%.

The clinical examination revealed no obvious facial asymmetry, no tender points in the masticatory or cervical muscle groups, and no pain on palpation of either temporomandibular joint capsular ligament. The results of the intraoral examination were normal except for pain elicited by percussion of the lateral bony cortex over the implant. Panoramic and cone beam computed tomography studies clearly demonstrated the encroachment of the implant on the superior cortex of the IAN canal (Figure).

Three-level quantitative sensory testing (QST) was directed to the right lip-chin receptor territory of the IAN. The unaffected left-side lip-chin stimulus responses served as normal controls. Level A QST with fine-touch stimuli from a camel-hair brush revealed mild loss of fine-touch detection functions on the right side; these same nonpainful stimuli elicited painful responses, a phenomenon known as *allodynia*. Level B crude pressure testing done with repeated punctate pressure from Semmes-Weinstein monofilaments also revealed mild sensory loss on the right side; these stimuli elicited mild radiating pain, a phenomenon known as *hyperpathia*. Level C QST with mild noxious pinches revealed pain detection bilaterally; however, the same mild pain stimuli invoked excessive pain responses on the affected side, or *hyperalgesia*, as compared to control lip-chin tissue responses. The QST results indicated that, while the patient was able to detect a range of stimuli, she had mild sensory deficits on the affected (right) side and her right-sided responses to all neurosensory test stimuli were hyperactive compared to the contralateral responses.

Given the neurosensory findings and the 20-month time span elapsing from the initial injury to the date of examination in the clinic, the prognosis for future spontaneous recovery without treatment was poor. After consultation with a restorative dentist, who determined that the implant was not restorable, the following course of treatment was recommended to the patient: medications (nonsteroidal anti-inflammatory drugs and gabapentin titrated to response), removal of the implant, surgical decompression with necessary nerve repair, and repositioning of the IAN at a lower level in preparation for possible future implant placement. Because the patient was actively nursing her child, she elected to postpone the use of any medications and surgery. A few days after her consultation, the patient relocated, and she was temporarily lost to follow-up.

Three months after her initial consultation with us, she called to report that she was experiencing pain in the uninjured left side of the mandible. She also noted continuation of her original right-sided pain. She reported that, in an effort to relieve her pain, she had undergone root canal treatment and the removal of 2 teeth on the left side. None of these treatments alleviated the pain. In addition, brushing her hair on the right side of her head and touching her eyelashes and face on the right side triggered tingling pain in her right lip-chin area.

A neurologist was consulted to rule out possible central neurologic disease, such as multiple sclerosis or an intracranial lesion, as the cause of her new, spreading pain presentations. The neurologist reported that the results of the examination were normal except that the patient exhibited both right- and left-sided jaw pain.

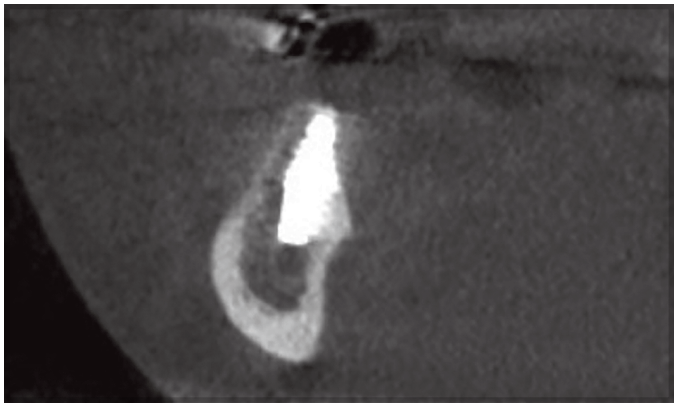


Figure. Implant engaging superior cortex of the inferior alveolar nerve canal.

After the neurologist reported that the patient demonstrated no signs of overt central neurologic pathosis, she underwent further evaluation by 3 general dentists, an endodontist, and a prosthodontist; none of these experienced practitioners found clinical or radiographic cause for her left-sided jaw pain. Based on the history, the presentation of symptoms, and the absence of other causes, the patient's condition was assigned a provisional comprehensive diagnosis: chronic spontaneous and evoked neuropathic pain with both ipsilateral and contralateral spread after partial traumatic injury to the right IAN. Chart 1 summarizes the details of evaluation, diagnosis, and management. The patient subsequently declined further surgical therapy and was referred to and is now under the care of a pain management specialist.

Discussion

Classification of nerve injuries

In 1951, Sunderland formulated a 5-level classification of nerve injuries based on the extent of axon degeneration and disruption of endoneurial, perineurial, and epineurial tissues following injury.[1] Type 1 nerve injury, as sustained in a mild crush or stretch injury, involves only the endoneurial tissue with little to no wallerian axon degeneration. Full spontaneous recovery is expected.

Type 2 injuries result from more forceful crush or traction injuries. Compression from implants that encroach on the superior cortex of the IAN canal may produce this level of injury. Some axonal degeneration may occur, but the endoneurium, perineurium, and epineurium remain intact. Axonal regeneration and sensory recovery are expected within 2-4 months.

Type 3 injuries result from a more severe mechanical crush that results in wallerian degeneration at the injury site and some cell loss in the nerve's central ganglion. The endoneurium is also damaged, and intraneural bleeding and scarring may interfere with complete axonal recovery and result in permanent neurosensory changes. An implant entering the IAN canal itself can cause this type of injury.

A type 4 injury involves destruction of endoneurial and perineurial tissues but leaves the epineurium intact. Neuroma formation can occur in a type 4 injury and is referred to as *neuroma-in-continuity* because of the intact epineurium. A type 5

injury connotes complete transection through the endoneurium, perineurium, and epineurium. Type 4 and 5 injuries require surgical repair.

Based on the radiographs and QST evaluation, the patient's injury was most likely a Sunderland type 3 crush injury to her IAN. Some Aβ light touch fibers and C pain fibers were either uninjured or had recovered, because she was able to detect a range of stimuli. At the same time, she experienced mild sensory deficits, and her responses to the stimuli on the right side were hyperactive compared to the contralateral IAN stimulus responses.

Mechanisms of neuropathic pain

The present case was characterized by 3 clinical neuropathic features: (1) spontaneous pain of 20 months' duration following partial trigeminal nerve injury; (2) evoked (triggered) hypersensitive pain presenting as allodynia, hyperpathia, and hyperalgesia; and (3) delayed spread of pain from the injured nerve distribution, including both ipsilateral (referred) and contralateral (mirror-image) symptoms. The neural mechanisms that explain these responses to nerve injury are based on neural plasticity and sensitization arising in both the peripheral and central trigeminal systems. The current understanding of plastic sensitization mechanisms contrasts with the historical cartesian model of a hard-wired and unchanging nervous system with fixed connections in which nerves transmit noxious signals and the brain receives and perceives pain in direct proportion to the strength of detectable inflammatory lesions.[2]

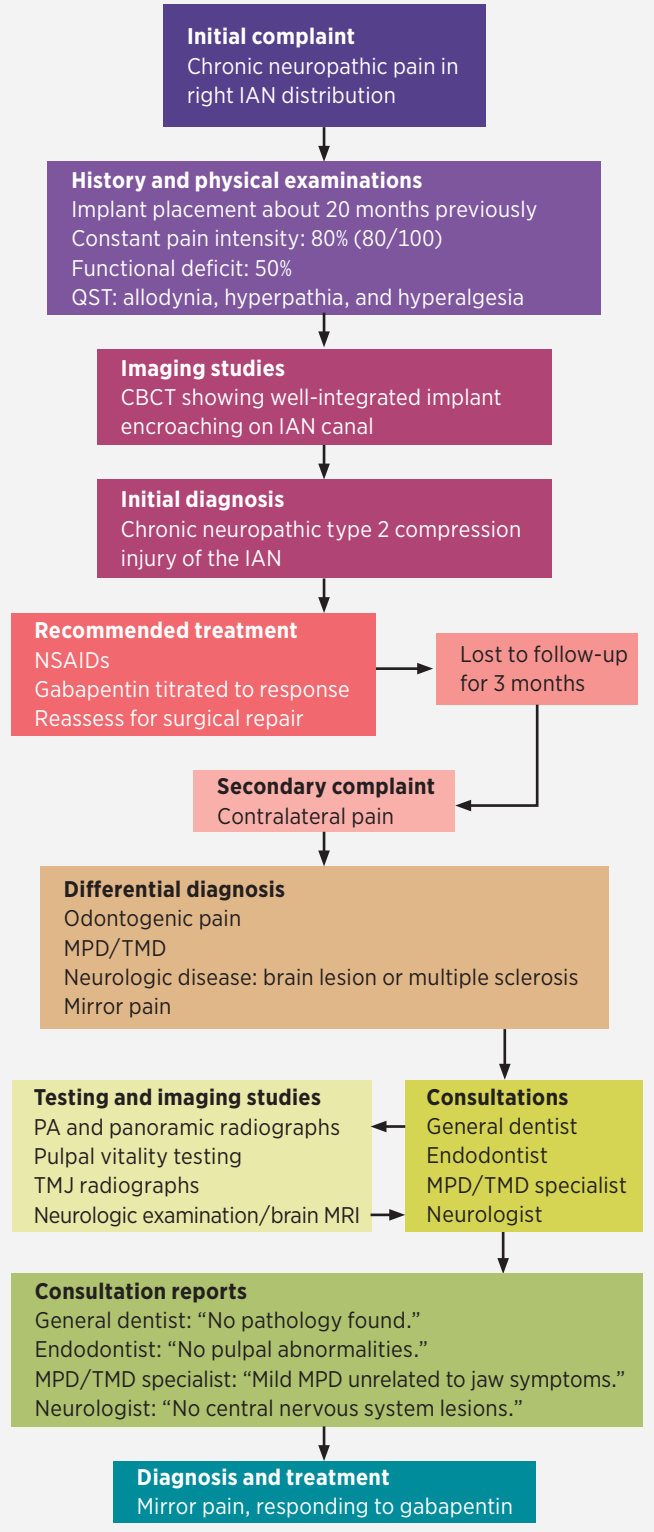
Chronic neuropathic pain

Because sensitivity and plasticity are changes in the nervous system that lead to the development of chronic pain, it is important to understand the underlying neural mechanisms of transition from acute postinjury neuropathic pain to chronic, sustained, and spontaneous neuropathic pain.

Acute pain events following less severe nerve injury, such as mild compression or a mild stretch nerve injury involving the nociceptor Aδ and C fibers, are usually self-limiting. Pain abates in a relatively short time, as healing and recovery of normal sensation take place. However, following more severe nerve injuries, such as crush injuries (as in this case) or injuries resulting in neuroma formation, the neuropathic pain can be ongoing. Sustained pain lasting 3 months or more after injury is arbitrarily considered "chronic." By the time chronic neuropathic pain has developed, changes in neural structure and function have occurred.[3] These neuroplastic changes result in a state of hyperactivity known as *sensitization*, which affects both the injured peripheral nerve complex and associated central nervous system (CNS) structures.[3]

After mechanical or chemical damage to trigeminal nerves, local inflammatory cell factors release pronociceptive mediators such as nerve growth factor and prostaglandins, among others. This acute neuroinflammatory response ordinarily reverses spontaneously over time. However, when the process does not spontaneously reverse, pain is sustained due to pathologic plastic changes in damaged trigeminal nociceptor fibers that are responding to epigenetic factors (alterations of gene expression) especially with a continued release of nerve growth factor.[4]

Chart 1. Summary of case management.



Abbreviations: CBCT, cone beam computed tomography; IAN, inferior alveolar nerve; MPD, myofascial pain-dysfunction; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; PA, periapical; QST, quantitative sensory testing; TMD, temporomandibular disorder; TMJ, temporomandibular joint.

A state of long-lasting hyperactivity of damaged nociceptors develops and helps explain the transition from acute inflammatory pain to sustained, chronic neuropathic pain. This phenomenon is known as *peripheral sensitization.*

However, to more fully understand how chronic pain may follow trigeminal nerve injury, *central sensitization* must also be considered.[3] Central sensitization develops when repeated noxious barrages from sensitized first-order neurons reach their second-order neurons in central synaptic pain centers.[5] In trigeminal nerve injuries, this is first seen in the brainstem and spinal trigeminal complex, also known as the *medullary dorsal horn* (MDH). It is also likely that the sensitized second-order postsynaptic trigeminal neurons in the MDH neurons project to and sensitize higher pain mediation centers in the reticular formation, thalamus, limbic system, and somatosensory cortex.[6,7] This is the overall state of central sensitization and reflects an increased excitability of central nociceptive neurons that has been induced by previous inflammation or nerve injury, resulting in chronic, sustained pain.

Accumulating research on the trigeminal nerve system has led to the consensus that a combination of both peripheral and central sensitization accounts for the development of sustained (chronic) neuropathic pain after peripheral trigeminal nerve injury in the absence of peripheral inflammatory lesions.[8]

Extraterritorial neuropathic pain

The spreading of pain beyond the initial site of injury is referred to as *extraterritorial pain.* Two forms of extraterritorial pain were found in the patient described in the present case report: ipsilateral referred pain (RP) and contralateral mirror pain.

Referred pain

The patient reported discomfort and tingling paresthesias in her right lip-chin region in response to nonnoxious touches on the right side of her face and head when brushing her hair, that is, stimuli over the distribution of the auriculotemporal nerve. Although the mechanisms of clinical RF are not completely understood, 3 concepts have been theorized: the convergence of varied nerve fibers on wide dynamic range central neurons, spread of regional glial activity, and structural "sprouting" of central neurons into injured, deafferented neural zones.

A wide range of intact nerve fiber types, including large A fibers, small myelinated Aδ nociceptor fibers, and visceral C pain fibers, are known to converge on wide dynamic range neurons within injury zones of the central MDH.[9] Because wide dynamic range neurons are rapidly acting with wide receptive fields, they are strong candidates for the mediation of spreading RP that is activated by glial sensitization.[10,11] Ipsilateral spread of RP attributed to glial activation occurs not only in the trigeminal MDH but also in the lateral thalamus, where connections to the overlying somatosensory cortex serve the sensory-discriminative dimension of RP and paresthesias after nerve injury.[12]

Research has also shown that nerve injuries may induce sprouting of synapse-like structures from intact neurons into adjacent regions of injured and necrotic central zones. Sprouting has been detected in primate somatosensory cortex, brainstem, and spinal cord subnuclei as well as dorsal root ganglia after deafferentating nerve injuries.[13-15] Hyperactivity in these sprouted regions may be an added basis for RP.

Mirror pain

Another major finding in this patient with implant injury was mirror pain: the spread of pain to the distribution of the uninjured contralateral nerve. Recent research has shown that peripheral nervous system mechanisms may contribute to the induction of MP. Cheng et al have shown that satellite glia (astrocytes and microglia) in contralateral dorsal root ganglia are influenced by proinflammatory factors such as tumor necrosis factor α and excess nerve growth factor that have been released by the injured nerves and have diffused from the injured side via cerebrospinal fluid.[10,11] Satellite glia in the contralateral dorsal root ganglia then react to these factors to increase excitability and generate MP.[4,16]

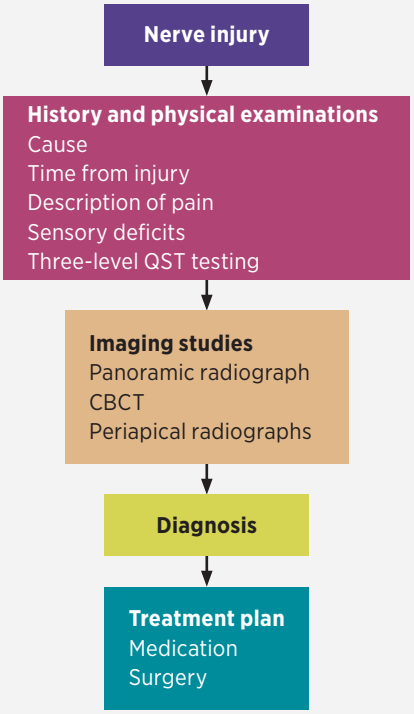
Central sensitization of forebrain regions also explains how neuropathic symptoms may spread contralaterally over time after nerve injury. The thalamus has been highlighted as a key locus for MP because ascending pain inputs from both sides of the body are known to converge there.[12] Functional magnetic resonance imaging studies have implicated both the ventrolateral and medial thalamus and their projections to the somatosensory cortex (SII) and limbic cortex as primary mediation sites for extraterritorial (contralateral) neuropathic pain, including allodynia.[17]

The prevalence of mirror-image neuropathic symptoms following trigeminal nerve injuries is unknown. Mirror pain has been a well-known phenomenon for many years, but the neural mechanisms that are involved are only now becoming better understood. Mirror pain has been commonly associated with chronic pain in patients with cancer, fibromyalgia, herpes zoster, and complex regional pain syndrome (formally referred to as *causalgia* and *reflex sympathetic dystrophy*).[10] In QST studies, contralateral paresthesias and mild hyperalgesia to pressure pain have been found in up to 57% of patients with peripheral spinal nerve injuries resulting in unilateral spinal neuropathic pain.[18,19] Research regarding the trigeminal nerve has shown that extraterritorial phenomena exist in experimental animal models.[20] Additionally, a study in humans has shown that healthy teeth that are contralateral to extracted, painful, symptomatic teeth have lowered thresholds to a mechanical stimulus.[21] However, clinical cases of extraterritorial posttraumatic pain and paresthesias after trigeminal injuries have been only infrequently reported, and no prospective or retrospective studies have been published, so the occurrence rate is unknown. As noted, a relatively high incidence of MP findings is associated with spinal nerve injury.[19] It is unknown whether the occurrence of extraterritorial symptoms after trigeminal injury is simply rare or the key diagnostic findings have been missed or misinterpreted and consequently are underreported.

Recommended management of nerve injury

Clinicians must consider that a state of neural sensitization, both peripheral and central, has developed when patients complain of chronic sustained pain, triggered excessive pain episodes, and extraterritorial spread of pain and paresthesia symptoms. Excess pain invoked by natural stimuli may take the form of allodynia

Chart 2. Evaluation protocol for suspected nerve injury.



Abbreviations: CBCT, cone beam computed tomography; QST, quantitative sensory testing.

(response to innocuous stimuli), hyperpathia (response to repetitive blunt pressures), and/or hyperalgesia (excess responses to noxious stimuli). Extraterritorial pain may take the forms of ipsilateral RP and/or contralateral MP, as seen in the present case. The patient's MP did not manifest until approximately 2 years after her initial injury. A time lapse between injury and pain symptoms is common, so a connection between the original injury and the MP may not be readily appreciated.

When establishing a differential diagnosis in a suspected case of MP, clinicians must rule out other serious CNS causes for the reported pain. Because of the patient's age, the possibility of multiple sclerosis, a brain lesion, or other CNS pathosis was a concern. As a result, she was referred for consultation with a neurologist, who performed a complete neurologic evaluation, including magnetic resonance imaging. No CNS abnormalities were found to be present.

In addition to CNS disease, the differential diagnosis included intrinsic temporomandibular joint disease, myofascial pain-dysfunction, or odontogenic sources of her pain. Prior to returning to the clinic for reexamination after moving, the patient underwent multiple endodontic procedures and extraction of 2 teeth in an attempt to alleviate her left-sided pain. At her return to the clinic, 3 general dentists, an endodontist, and a prosthodontist were consulted. None of these professionals established temporomandibular joint, myofascial, pulpal, or other odontogenic causes for her pain. Unless there are clear indications of inflammatory odontogenic pathosis, clinicians should avoid invasive procedures such as endodontic treatments or extractions and consider the possibility that extraterritorial pain is present.

When a nerve injury occurs, it is important for clinicians to respond quickly and appropriately (Chart 2). If the injured nerve is observed to be transected (Sunderland type 5 injury) or severely crushed (type 3 injury), the patient should be immediately referred for consultation on surgical nerve repair. In most cases, however, the injured nerve is not directly visible, and the clinician is not aware of the injury until the patient complains about a loss of sensation. Once the dentist becomes aware of a nerve injury, the patient should be evaluated and a baseline of the areas and extent of sensation loss should be documented. This information can be recorded on a simple sketch of the lips and chin that shows the patient's response to a series of light pinprick stimuli.

Testing for nerve responses to various stimuli should be performed while the patient's eyes are closed and does not require special equipment or devices. Responses to directional stimuli can be determined by using cotton filaments and pressure with a mirror handle. Pain responses can be observed by gently squeezing the vermilion border with a hemostat or cotton pliers. All responses should be compared to responses on the opposite unaffected side.

A patient's individual neurologic and psychological responses to a nerve injury vary. The dentist should demonstrate concern, be sympathetic, and remain connected to the patient. After a baseline is established, the following schedule is suggested:

- The patient should be followed at 2-week intervals for the first month to assess for any changes.
- If there is no significant improvement at 1 month, the patient should be reevaluated in 3 months (4 months after initial presentation).
- If there is no improvement in 3 months (4 months after initial presentation) and the patient remains totally anesthetic, has lost protective reflexes (eg, exhibits lip or cheek biting), complains of drooling, has speech impediments, or reports a general loss in quality of life, referral for evaluation by a specialist in microsurgical repair should be considered.
- Alternatively, if there is no improvement in 3 months but the patient is otherwise stable, he or she can be followed every 3 months for the next 6 months.
- After that point, the stable patient can be followed at 6-month intervals until a plateau is reached.

Times for spontaneous nerve recovery are variable and dependent on the nature and extent of the injury. Recovery can take 3-9 months if improvement begins before 3 months. However, if improvement ceases to progress, it rarely will begin again. Watchful monitoring is generally acceptable *in the absence of pain* and when there are objective signs of continually progressing, neurosensory functional recovery.

If neuropathic pain accompanies or develops after acute nerve injury, medical treatment should begin immediately. Because opiate analgesics have proven only marginally effective in treating emerging chronic neuropathic pain, centrally acting agents such as gabapentin or pregabalin with an antidepressant co-medication should be prescribed instead.[22,23] Early surgical consultation may also be indicated in such cases, as

approximately 60% of patients with trigeminal posttraumatic pain experience some or complete pain relief after early reparative surgeries.[24] While each patient should be evaluated individually, the ideal time for surgical repair of an injured nerve is within the first 3 months following the injury.

Conclusion

The overall goal in treatment of painful trigeminal nerve injuries is to prevent the transition from acute inflammatory pain to chronic centrally sensitized neuropathic states with all their potential sequelae. Consequently, clinicians need to begin effective, early pain management to prevent the changeover to chronic pain that has become centralized and refractive to treatment.

Author information

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