Neuropathic pain in the trigeminal system

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# Case Study

A 69-year-old woman with a history of arterial hypertension and COPD presents with pain symptoms in the right infraorbital area. These pain complaints have been present for 10 years. Upon further inquiries they appear to have arisen after a routine dental visit during which a premolar in the upper jaw was removed. Initially there was severe pain after the operation with a fuzzy swollen feeling under her right eye. The dentist told her this would heal spontaneously, but it didn't. At subsequent checks he said he had never seen this before and referred her back to her general practitioner.

At present, she describes the pain as continuously burning and tingling, scoring 8 out of 10 on a VAS scale. In cold weather the burning sensations become unbearable. She also complaints of intermittent headaches. She already saw several specialists. At several occasions, imaging studies and biopsies were taken which were all inconclusive. She tried numerous medications (pregabalin, amitriptyline, duloxetine, oxycodone), but no therapy gave her a meaningful improvement of the complaints. On top of that, they made her feel very tired and dizzy. No one has been able to make a clear diagnosis of her problem so far. Indeed, there is nothing remarkable on clinical inspection. The patient is desperate and shows clear signs of depression. For this the GP recently started escitalopram.

# Diagnostics

The above case describes a typical story of a patient with post-traumatic trigeminal neuropathic pain (PTNP). Neuropathic pain has been recently redeﬁned as pain arising as a direct consequence of any lesion or disease aﬀecting the somatosensory system (Haanpää et al., 2011). Apart from being post-traumatic, the most common diseases related with neuropathic pain are diabetes, HIV, multiple sclerosis and chemotherapy which rarely occur in the head and neck region (Colloca et al., 2017).

Recently, the first edition of the International Classification of Orofacial Pain (ICOP) was published accompanied by its diagnostic criteria.(“International Classification of Orofacial Pain, 1st Edition (ICOP).,” 2020). Post-traumatic trigeminal neuropathic pain was defined as unilateral or bilateral facial or oral pain caused by trauma to the trigeminal nerve(s), with other symptoms and/or clinical signs of trigeminal nerve dysfunction and persisting or recurring for more than 3 months. The diagnostic criteria are summarized in Table 1.

Table 1. Diagnostic criteria of post-traumatic trigeminal neuropathic pain according to the recent ICOP version 1.

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| Previously used terms: anaesthesia dolorosa; painful post-traumatic trigeminal neuropathy. |
| A. Pain, in a neuroanatomically plausible area within the distribution(s) of one or both trigeminal nerve(s), persisting or recurring for >3 months and fulﬁlling criteria C and D |
| B. Both of the following: |
| 1. history of a mechanical, thermal, radiation or chemical injury to the peripheral trigeminal nerve(s) |
| 1. diagnostic test conﬁrmation of a lesion of the peripheral trigeminal nerve(s) explaining the pain |
| C. Onset within 6 months after the injury |
| D. Associated with somatosensory symptoms and/or signs in the same neuroanatomically plausible distribution |
| E. Not better accounted for by another ICOP or ICHD-3 diagnosis. |

Tests that are considered valid to diagnose PTNP are radiographic or surgical confirmation of nerve injury, nerve conduction study, laser-evoked potentials, blink tests, skin biopsies showing reduced nerve fibre terminals. However, all clinical and diagnostic aspects should be considered. An important side note: radiation-induced nerve injury may appear beyond 3 months after irradiation but is still considered post-traumatic trigeminal neuropathic pain, hence the large window of onset considered.

## Clinical assessment

When assessing patients with surgically induced nerve injuries we recommend a holistic approach (Tara Renton & Van der Cruyssen, 2019). We must treat the patient with the nerve injury, not just focus on the nerve injury itself. Many of these patients have experienced an unexpected traumatic event which demands a thorough history taking and examination including attention for sensory testing and psychological assessment. These elements are necessary both in diagnosis and in the choice of therapy.

The intensity of pain and treatment effect (both in clinic and trials) should be assessed with numerical rating scale or visual analogue scale. For future neuropathic pain trials, pain relief scales, patient and clinician global impression of change and the proportion of responders (50% and 30% pain relief) are important measures. Pain may be reported to be moderate to severe intensity. The pain characteristic is often reported as constant or intermittent burning or elicited and or spontaneous neuralgia. Most cases are continuous, but may report superimposed paroxysmal pain attacks (Benoliel et al., 2012). The pain may be short lasting and neuralgiform elicited due to touch or thermal change usually to cold, in the neuropathic domain, mimicking trigeminal neuralgia (Renton T et al, 2011). Pain is usually unilateral, unless bilateral procedures have successfully injured the patient bilaterally, and may be precisely located to the dermatome of the aﬀected nerve with demonstrable sensory dysfunction. The trigeminal dermatomes are illustrated in Figure 1.

Afbeelding met tekst, kaart

Automatisch gegenereerde beschrijving

Figure 1. The trigeminal nerve and its dermatomes.

The authors believe that the neuropathy develops immediately after trauma, unless related to endodontic procedure where there may be a 2-3 days delay in neuropathy development. A standardized clinical mechanosensory assessment is illustrated in Figure 2 (source: (Tara Renton & Van der Cruyssen, 2019). These clinical mechanosensory tests have been shown to have a high speciﬁcity however they have a low sensitivity (Zuniga et al., 1998). For more accurate sensory profiling, quantitative sensory testing (QST) is recommended for selected cases in clinic, including the diagnosis of small fiber neuropathies and for research purposes (Haanpää et al., 2011). Advanced neurophysiological testing is superior to clinical testing (Teerijoki-Oksa et al., 2019), but this is not always possible intraorally or in large trials involving patient populations. The use of brainstem reﬂexes and advanced neurophysiologic testing will accurately establish nerve damage (Jääskeläinen, 2004).

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| Examination protocol for mechanosensory evaluation of the extraoral dermatome of V3. This protocol could also be applied to other dermatomes. | |  |  |
| Area affected  Using forceps run over normal to neuropathic area warning the patient that there may be hypersensitivity as well as hyposensitivity.  Map out the area and record pictorially or by photograph using pen marks on patient's face.  Estimate the % or extra-oral dermatome is affected by the neuropathy.  (yellow dotted lines indicate V3 dermatome and arrows indicate direction of testing from normal to neuropathic area) | Afbeelding met man, persoon, stropdas, dragen  Automatisch gegenereerde beschrijving  Afbeelding met persoon, man, dragen, stropdas  Automatisch gegenereerde beschrijving | **Sharp blunt discrimination**  Using a dental probe sharp and blunt ends, the unaffected side is tested first. A minimum of five stimulations would be used and the number recognized by the patient (if less than 3 out of 5 then the test is negative). Whilst this test can illustrate hypoaesthesia with reduced sharp detection on the affected side, this test can also identify mechanical hyperalgesia (increased pain on sharp stimulation) which is often extremely uncomfortable for the patient. Sharp thresholds can be estimated using specially designed algometers not used in this study. | Afbeelding met persoon, man, stropdas, dragen  Automatisch gegenereerde beschrijving  Afbeelding met persoon, man, stropdas, dragen  Automatisch gegenereerde beschrijving |
| Subjective function  Using forceps with beaks together firmly tap (minimum 5 times) the patient's hand several times explaining that is 'normal' 10 out of 10 subjective function. Then tap, with the same pressure, over the unaffected side of the face or tongue and repeat the stimulation explaining that should be 10 out of 10.  Move your forceps away and explain no stimulation at all is 0 out of 10. Repeat over neuropathic area that you have already confirmed and ask the patient to report the level of stimulus. Everything that feels painful or hyperaesthetic is reported higher than 10 with 20 being the worst stimulus intensity imaginable. Everything that feels hypoesthetic is reported lower than 10 with 0 being anesthetic.  This test can be repeated over different domains of the neuropathy (lip vermillion, lip skin and chin skin or over tongue) | Afbeelding met persoon, man, dragen, binnen  Automatisch gegenereerde beschrijving | **Two-point discrimination (TPD)**  Using college forceps with beaks open and closed (both for five stimulations), TPD function can be estimated. Some authors prefer specially designed calipers which can be set to a specific distance. Normal TPD in the V3 dermatome extraorally ranges from 2-4mm on the lip vermillion to 6-8mm on the skin of the chin.  **Light touch**  To evaluate light touch thresholds von Frey filaments are highly recommended. If these are not be available, a pledget can be used instead, placing repeated (minimum 5 times) on normal side first then repeated on affected side; ask the patient to report differences. If the patient is experiencing numbness on stimulation, they will have reduced light touch detection thresholds. However, if the patient is suffering from hyperaesthesia and possible allodynia (pain on touch) this test can be very uncomfortable. | Afbeelding met persoon, man, dragen, stropdas  Automatisch gegenereerde beschrijving  Afbeelding met persoon, man, dragen, stropdas  Automatisch gegenereerde beschrijving  Afbeelding met persoon, man, dragen, stropdas  Automatisch gegenereerde beschrijving |

There is almost always an area of abnormal sensation (with the exception in trigeminal neuralgia which is NOT post-traumatic) and the maximum reported pain is associated with the area of sensory deficit (i.e. suffering from a mixture of pain, numbness and altered sensation). This is an important diagnostic feature for sensory nerve neuropathy. Commonly used descriptors are illustrated in Table 2.

Table 2. Commonly used descriptors and their definition (source: IASP).

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| **Descriptor** | **Definition** |
| Negative symptoms | |
| Anaesthesia | Complete absence of sensation to stimuli |
| Hypoesthesia | Reduced perception of nonpainful stimuli |
| Hypoalgesia | Reduced perception of painful stimuli |
| Thermo hypoesthesia | Reduced perception of heat |
| Positive symptoms | |
| Spontaneous pain | |
| Paraesthesia | Nonpainful tingling sensation |
| Paroxysmal pain | Shooting pain that occurs intermittently for seconds at a time |
| Causalgia | Sustained burning pain, allodynia, hyperpathia can be combined with vasomotor or sudomotor dysfunction and trophic changes |
| Dysesthesia | Unpleasant abnormal sensations, spontaneous or evoked |
| Stimulus-induced pain | |
| Allodynia | Pain induced by a nonpainful stimulus |
| Hyperalgesia | Increased pain by a painful stimulus |
| Hyperpathia - Summation | Increasing amounts of pain due to a repetitive stimulus |

Neuropathic pain commonly presents with allodynia (pain on non-noxious stimuli) hyperalgesia (increased pain to a noxious stimuli) and hyperpathia (continued altered sensation or pain after stimulation ceases). In 50-70% of patients report a combination of numbness, altered sensation and pain is experienced, the pain may be either spontaneous ongoing pain, which often had a burning character, and spontaneous shooting, electric shock-like sensations (neuralgia).Evoked pain due to touch or cold often leads patients to having difficulties with daily function, such as eating, socialising, kissing, speech, and drinking (Fréderic Van der Cruyssen et al., 2020).

Validated neuropathic pain quality measures including Douleur Neuropathique-4, PainDetect and LANSS questionnaires are able to qualify the presence of neuropathic pain but the sensitivity and specificity is reduced in the trigeminal region due to questions around pain wearing clothes and when having a bath for example (Smith et al., 2013)*.*

As a consequence, patients are often anxious, tearful and had psychological repercussions of surgery. These symptoms were often compounded by the lack of informed consent, which was given by only 30% of patients, most of whom were not specifically warned about potential nerve injury (Smith et al., 2013). The presence of anxiety or depression has been suggested to negatively affect treatment outcomes in other pain conditions. In striving for better outcomes, it is therefore advisable to also pay attention to the psychological impact. Psychological assessment requires the use of validated questionnaires exploring anxiety, depression, post-traumatic stress disorder, prior abuse and neglect, sleep quality, catastrophising and somatisation.

## Radiological investigations

Routine panoramic radiography is necessary in assessing if after dental extractions the roots remain adjacent to the inferior alveolar nerve and these require removal providing an opportunity to explore and repair the nerve if necessary. Cone beam CT scanning will be required to further assess the relationship between the roots and the mandibular canal which contains the inferior alveolar nerve (Dessouky et al., 2018). Neither medical CTs or MRIs are of great assistance in assessing nerve injuries. However, there are some emerging imaging technologies such as magnetic resonance neurography or multimodal assessments can aid in further diagnostics (Chhabra et al., 2011; Frederic Van der Cruyssen et al., 2020). Radiography after local anaesthetic nerve injuries is of no benefit and both endodontic and implant treatments should be completed with a post-surgical radiograph thus no further radiation is required.

# Therapy

Evidence base remains limited for managing dental related nerve injuries and related PTNP, many are permanent and there is no ‘magic bullet’ to fix them (Coulthard et al., 2014). If the patient reports numbness, altered sensation and or pain, reassure them, acknowledge their complaints without minimising and arrange review. The singular consensus is that prevention of these nerve injuries is possible and optimal. The patient with the nerve injury must be treated, not the nerve injury in isolation. The neuropathy with associated functional and psychological impact will be the driving force behind the patient seeking treatment (Tara Renton & Van der Cruyssen, 2019). These factors must be assessed and the potential outcomes, good or bad, be discussed and agreed with the patient. Decision on managing the patient with a nerve injury is based upon the holistic assessment of the patient. The clinician must assess the degree and impact of the nerve injury and the type of patient. Some patients may present with large painful neuropathies but are happy to continue as is with minimal life impact, whereas others may present with small areas of neuropathy with no pain but signiﬁcant related functional and psychological impact. As with all decisions in life there are beneﬁts and risks with any intervention. No reparative surgery or chronic pain medication is devoid of side effects or potential risks. The patient has to be made aware of the diagnosis, prognosis and possible interventions with associated risks and beneﬁts. This is a long conversation and may need to take place over several consultations.

Management of PTNP will depend upon the presentation of the patient (pain, functional and psychological implications) duration and cause of the nerve injury (T. Renton, 2013; T. Renton & Yilmaz, 2012).Table 3 summarises the management and timing of intervention for trigeminal nerve injuries based upon the current evidence base.Urgent care is initiated as soon as possible after presentation.

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| Urgent care includes:   * Homecheck - If you cause pain during an Inferior dental block (IDB), implant or endodontic or surgical extraction treatment follow them up the next day and check they are OK. If the patient reports numbness, altered sensation and or pain reassure them. Endodontic nerve injuries may take 2-3 days to develop which may be due to chemical leakage of high pH chemical used for cleansing the dental pulpal chamber leaking out of the apex of the tooth. * Continue to support and reassure your patient and advise them to visit to confirm the presence of neuropathy. If the neuropathy affects most of the dermatome +/- associated with severe neuropathic pain nerve injury must be suspected. Reassure your patient that 75% of these injuries resolve. * Say SORRY as this is NOT an admission of guilt * Initiate medical management (recommended for other peripheral sensory nerve injuries)   + High dose oral NSAIDs (400-800mgs Ibuprofen PO QDS) for 2 days only. Bandolier Oxford league table summarises the optimal analgesia for post-operative pain and combined Ibuprofen and paracetamol have the smallest number needed to treat   + GMP prescription for Prednisolone 5 day step down does 50-40-30-20-10mg PO (not for patients with contraindications for steroids or NSAIDs)   + Vitamin B complex (Riboflavin 400mg once daily for maximum of 3 months plus other Vit B complex) * Arrange a review of the patient. |

The management may include patient reassurance and education, medical, surgical and/or psychological treatments. Patients sustaining local anaesthesia, orthognathic, oncology and trauma related nerve injuries will mainly be managed therapeutically. Surgical treatment is rarely indicated unless in urgent situation. Urgent surgical intervention should be recommended for known or highly suspected nerve injury, and those related to endodontic or implant nerve injury. Later surgical intervention for hypoaesthetic nerve injuries does not return the patient to normality and surgery for patients with pain and hyperaesthesia is often not indicated as the pain is not abated and patients are faced with long term antiepileptics or antidepressants for chronic pain (Kushnerev & Yates, 2015; Zuniga et al., 2014; Zuniga & Yates, 2016).

Counselling is the most useful effective tool for managing patients with problematic permanent sensory nerve injuries. As previously stated, the assessment of axis 2 is imperative in holistic patient care. Psychological interventions may include cognitive behavioural therapy, acceptance and commitment therapy, mindfulness, meditation, group of individual counselling depending upon the patient’s needs.

Table 3. Algorithm for management of trigeminal nerve injuries.

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| **Etiology of nerve injury** | **Time since injury** | **Treatment** |
| Known or suspected nerve injury |  | **Immediate exploration** |
| Wisdom tooth surgery with retained roots | < 30 hours | **Immediate exploration** |
| Dental implant placement | < 30 hours | **Immediate exploration** |
| Endodontic treatment | < 30 hours | **Immediate exploration** |
| Implant placement or endodontic treatment | > 30 hours | Pharmacological |
| Wisdom tooth surgery with inferior alveolar nerve injury, dysesthesia, large neuropathic area, considerable impact on QoL | < 3 months | Consider exploration |
| Wisdom tooth surgery with lingual nerve injury, large neuropathic area, pain, loss of taste | < 3 months | Consider exploration |
| Wisdom tooth surgery | > 6 months | Pharmacological, psychological |
| Local anesthesia, trauma, orthognathic surgery | > 6 months | Pharmacological, psychological |

## Pharmacological treatment

Pharmacological treatment is indicated for patients with pain or discomfort or with anxiety and or depression in relation with chronic pain. However, due to the multiple noxious side effects of chronic pain medication, <18% of patients remain adherent with medication (Finnerup et al., 2015).

### Systemic treatment options

The mainstay of neuropathic pain pharmacotherapy remains the antiepileptic and tricyclic antidepressant drugs with widely accepted protocols (Finnerup et al., 2015). Treatment of chronic neuropathies often requires long-term prescription medications that have signiﬁcant side eﬀects. The use of nonsteroidal analgesics and opioids is particularly common, on the other hand antiepileptic drugs and tricyclic antidepressants are relatively uncommon (McDermott et al., 2006). This is surprising in view of the higher eﬀectiveness of these drugs in neuropathic pain and suggests that patients may not be seeking treatment or are inadequately managed. It is not unusual for patients to switch over to alternative medicine, and many report the use of vitamins and supplements (McDermott et al., 2006).

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| **National institute clinical excellence (NICE) recommendations for prescribing for adult neuropathic pain (2016).**  All neuropathic pain (except trigeminal neuralgia):   * Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia) * If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated. * Consider tramadol only if acute rescue therapy is needed * Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments. |

New drugs targeting novel mechanisms include, subtype selective sodium channel-blocking agents, particularly Nav1.7 antagonists, and EMA401, a novel angiotensin type II antagonist that have been found to be effective in a phase II clinical trial in postherpetic neuralgia (Li et al., 2019; Rice et al., 2014). Although still in the preclinical phase, studies show promising results of stem cell treatment for neuropathic pain (Fortino et al., 2013).

### Local treatment options

Topical application aims to induce a high local concentration of the active drug at the aﬀected site with minimal or no systemic absorption. Drug interactions are reduced, of beneﬁt to patients on multiple drugs or when speciﬁc side eﬀects are problematic. Moreover, local application is easy to use and requires no dose titration commonly needed in systemic therapies (Sawynok, 2003). Localized reactions such as rash are uncommon, but some topicals (e.g., capsaicin) may induce local pain on application. Intraorally, the use of topical agents is relatively complex and requires either prolonged isolation of the area or the construction of an intra oral appliance that will allow optimal concentrations

A positive eﬀect has been observed for topical capsaicin in a heterogeneous group of patients with oral neuropathic pain (Argoff, 2006). However, in a recent systematic review, it was concluded that although topical capsaicin has only poor to moderate eﬃcacy in the treatment of neuropathic pain, it may be useful in some cases resistant to other modes of therapy or as adjunct therapy (Mason et al., 2004). More recently, a combination of topical drugs has been successfully applied to the treatment of oral neuropathies (Heir et al., 2008). The authors concluded that topical medication as single treatment or in combination with systemic medications can reduce orofacial neuropathic pain severity.

## Surgical intervention

If surgery is undertaken, it is marginally more successful in inferior alveolar than in lingual nerve injuries (Pogrel, 2002; Ziccardi et al., 2009), but the presence of a neuroma is a negative prognostic factor (Susarla et al., 2007). Case series with repair within one year of injury show good success rates, as measured by sensory recovery (Caissie et al., 2005; Rutner et al., 2005; Strauss et al., 2006; Susarla et al., 2007; Ziccardi & Steinberg, 2007). About 50% of repaired cases will recover with complete sensory function by seven months (Susarla et al., 2007). However, the eﬃcacy of surgery for painful trigeminal neuropathies is unclear. This would also depend on the type of surgery performed, that is, nerve repair or interventional surgery to further remove pathology.

Allografting using a pre-prepared human treated cadaveric allograft for repair of the inferior alveolar and lingual nerve allows for repair with minimal tension. This is undertaken using microscopy and described in several publications (Salomon et al., 2016; Zuniga, 2015). This is likely to be the treatment of choice if repair is indicated and direct re-anastomosis cannot be undertaken most commonly for the inferior alveolar nerve. One of the main issues regarding nerve repair is the early identiﬁcation of the neuroma relating to the patients’ symptoms, and the connectivity of the nerve itself, that is, is the nerve actually functioning. Recent developments with magnetic resonance neurography have availed the surgeon to identify the nerve lesion and neural functionality to facilitate appropriate and earlier nerve repair intervention.

## Interventional therapies

Anecdotal evidence suggests that non neuro-ablative techniques should first line. However, neuro-ablative techniques include; glycerol injections, cryotherapy, balloon compression, thermocoagulation and other central procedures may be useful for recalcitrant cases (Bullard & Nashold, 1997; Kanpolat et al., 2005). The authors suggest that the primary choice of operation should be minimally invasive, such as computed tomography-guided percutaneous trigeminal tractotomy–nucleotomy (surgical division of the descending ﬁbers of the trigeminal tract in the medulla) eﬀectively ablating pathways that carry sensation from the face.

# Differential diagnostic challenges

## Chronic post-surgical pain or painful-post traumatic neuropathic pain?

Over 30-40% of patients presenting in chronic pain clinics are being diagnosed with CPSP (Bruce & Quinlan, 2011). CPSP is associated with many surgical procedures including; limb amputation, breast surgery, thoracotomy and herniorrhaphy. CPSP of the trigeminal system has been reported following most dental procedures. Lobb and colleagues reported that most patients suffering from phantom tooth pain did not return to the dentist, hence the likelihood that many dental surgeons underestimate chronic pain after their routine procedures (Lobb et al., 1996).

Chronic post-surgical pain with neuropathic area within the trigeminal system is given many names (post-traumatic trigeminal neuropathy, persistent idiopathic dentoalveolar pain, atypical odontalgia, phantom tooth pain). These may all be chronic post-surgical pain; however, many patients present without a neuropathic area necessary for a PTNP diagnosis. PTNP is not difficult to diagnose in relation to onset, often a traumatic event (third molar surgery, implant placement, local anaesthetic blocks and endodontic treatment). A neuropathic area may not be immediately apparent but is included the in ICHD3 diagnostic criteria. Elicited acute neuralgic pain to non-noxious stimuli (eating, tooth brushing, tooth tapping, cold) are features of PTNP and hence easily confused with various forms of toothache, primary headaches with neuralgic features (TACs) and trigeminal neuralgia, however, there are validated neuropathic pain screening for PTNP (LANSS, NPQ, DN4, PainDetect) which may assist the clinician in differentiating neuropathic pain from neurovascular pain.

## Trigeminal neuralgia

Secondary trigeminal neuralgy may be due to demyelination in patients with multiple sclerosis or other diseases of the primary and or central nervous system. Trigeminal neuralgia is the most frequent cranial neuralgia, yet is a rare entity with reported incidences of 4.5 per 100,000, far lower than post-traumatic trigeminal neuropathy, more prevalent in females, and occurs more common in the 50–70-year-old age group (Zakrzewska & Linskey, 2014). Trigeminal neuralgia mainly presents in the second and third dermatomes of the trigeminal nerve. The elicited, short lasting sharp, shooting, shock-like, burning and excruciating pain often starts spontaneously, lasting seconds and is often mistaken for toothache. The elicited neuralgic pain on eating, brushing teeth mimics cracked tooth, dentine hypersensitivity, reversible pulpitis. As the onset is usually after 50 years, the patients are also likely to have a heavily restored dentition making diagnosis of odontogenic pain more likely. Differential factors include pain that is likely to be elicited by extraoral sites, refractory period with cessation of elicited pain on continued stimulation. The clinician must reflect on the history presentation and non-response to routine care. They must take a step back and use their pain history to guide their diagnosis rather than relying on investigations, particularly radiographs.The aetiology and pathophysiology of classic trigeminal neuralgia remains unknown, but is hypothesised to be due to the compression of the trigeminal root at or near the dorsal root entry zone by a blood vessel. Using ultra-high-filed MRI a neurovascular conflict may be present in both symptomatic and asymptomatic, healthy individuals, warranting careful interpretation of MRI results (Zakrzewska & Linskey, 2014).

## How can other causes of secondary neuropathic pain mimic toothache or vice versa?

***Diabetic peripheral neuropathy*** often affects patients with diabetes. This condition often presents in the lower limbs and has characteristic neuropathic features (numbness, tingling, poor balance and burning pain). The mechanism of diabetic neuropathic pain is unknown, and rarely affects the trigeminal system.

***HIV-associated sensory peripheral sensory neuropathy*** (HIV-SN) is a common complication of treated or untreated HIV infection. HIV patients may be more at risk from Herpes Varicella Zoster infections causing herpes zoster and post herpetic neuralgia in the orofacial region.

***Postherpetic neuralgia (PHN)*** Herpes zoster virus when reactivated (shingles) can cause neuropathic pain in the trigeminal region. PHN commonly presents in the ophthalmic branch of the trigeminal nerve with an annual incidence 3-4 per 10,000 population If the patient becomes immunocompetent (due to increasing age, HIV infection, cancer or immunosuppressive therapy), the virus can reactivate causing hypersensitisation (hyperexcitability) and loss of sensation, deafferentation (sensory nerve death or damage).

***Chemotherapy-induced peripheral neuropathy (CIPN)*** Chemotherapy for cancer frequently causes neurological complications which are dose-dependent and rarely presents in the trigeminal system. The drugs most neurotoxic include; platinum drugs, vinca alkaloids, bortezomib and taxanes. Patients with CIPN report characteristic neuropathic pain symptoms of pain and numbness but often as symmetric and distal, with a “glove and stocking” distribution which rarely affects the trigeminal region. In most cases, CIPN improves after the therapy; however, with cisplatin and oxaliplatin, neuropathic pain may be progressive.

***Sickle cell disease or central and peripheral pathology causing secondary painful neuropathy***

Non iatrogenic causes of trigeminal neuropathic pain in 372 patients was 10.5%. These were caused by malignancy (20%), and infection (40%). Rarer causes included; sickle-cell anaemia, Paget’s Disease and multiple sclerosis, highlighting the importance to the clinician of considering differential diagnoses and urgent referral when indicated.

# Summary

Post-traumatic trigeminal neuropathic pain may be caused by many dental and oro-maxillofacial procedures and have a significant impact on our patients. Diagnosis can be difficult due to referral delay and interim numerous misguided interventions or investigations. Additionally, comorbid and mimicking pain conditions are common. International diagnostic criteria are available and should be implemented in everyday practice. Many therapeutic options are available. Unfortunately, none of these interventions’ ‘fix’ the patient, but the aim is to manage their symptoms as best as possible, improve function and allow them time to accommodate to these unfortunate events, which is often not very satisfactory. This chapter was intended to acknowledge and share some key issues around iatrogenic trigeminal nerve injuries resulting in post-traumatic trigeminal neuropathic pain and to provide some key take home messages.

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| **Take home messages**   * Neuropathic pain as well as altered sensation and numbness is what most patients experience with iatrogenic sensory nerve injury. This has a significant and unpleasant effect on the patient (improve your consent!) * The majority of iatrogenic trigeminal nerve injuries are avoidable * Inferior alveolar nerve injuries in relation to implant and endodontic dentistry are painful and permanent. They can be optimally reversed when treated quickly within 30 hours. * Owing to the significant problems following nerve injury, pre-operative strategies for minimizing this risk of nerve damage need to be considered carefully. Peri-operative planning, operative execution and post-operative care needs improving to minimise and hopefully abolish these injuries * There is a need for a consensus and standardisation of risk assessment and management, a holistic approach in managing the neuropathic pain, related effect on functionality and psychological implications caused to the patients affected by iatrogenic nerve injury. |

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