Orofacial peripheral neuropathic pain - mechanisms, diagnosis, treatments and treatment outcomes

Babak Soleymani and Golsara Mehryar
Odontologiska institutionen
Karolinska Institutet

Abstract

Neuropathic pain is defined by IASP as “pain initiated or caused by primary lesion or dysfunction of the nervous system”. It is indeed an important area of interest for practicing dentists in particular, as it may emerge as a result of dental treatment among other things. NP causes a lot of suffering among a large number of patients throughout the world. Thus, it also attracts a large amount of research. This project initially aimed to investigate what type of orally and topically given medications may alleviate orofacial peripheral neuropathic pain, based on a database of 53 unidentified/unnamed patients who had been diagnosed with central or peripheral neuropathic pain disorders; and also to discuss the paradigms or the current concepts in this area. However, as the database is still being updated, a number of important variables seemed to be missing and in addition, a significant number of the listed subjects had also been diagnosed with central neuropathic pain, we decided to select and present nine cases more detailed. A significant number of these cases showed an alleviated pain following treatment with anticonvulsant oral medications as well as topically administered Capsaicin and Orabase. Current and older research, however reports that antidepressants are the primary pain decreasing medications for NP. There are a number of other medications used today against NP; among these are anticonvulsants, locally acting analgesics (i.e. Capsaicin). As this field of pain still has a lot of unknown corners, and extensive research is underway as to what type of medications give the best outcome.

Introduction

Pain is defined by IASP (International Association for the Study of Pain) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. (1). This system is the most internationally used one, but there are also other classifications present more specific to orofacial pain, for example the International Headache Society system and the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). The advantage of the IASP system is that it is multiaxial with 5 axis; region, system, temporal characteristics, patient’s statement of intensity and etiology (2).

Pain exists in different types and different forms, but no matter what kind of pain one can distinguish two main components. First, the subjective assessment of the intensity, location and duration of pain, and second the affective part in which the emotional perception of pain is included. The intensity of the pain felt is affected by surrounding conditions, and the same stimulus can produce different responses or reactions in different individuals under the same conditions. One fact that makes it difficult both to define and to treat pain is this highly individual and subjective nature it possesses (3).

The IASP definition of neuropathic pain (NP) is “pain initiated or caused by primary lesion or dysfunction of the nervous system”. This definition has been criticized by many for the lack of specificity, especially concerning the use of the word “dysfunction” (1). For an explanation of expressions associated with different pain conditions see appendix 1.
Mechanisms of pain

In different tissues of the body there are receptors which respond to different stimuli, i.e. thermal, mechanical, chemical and polymodal stimuli. There is also a fifth group called silent nociceptors, which if activated may contribute to central sensitization and secondary hyperalgesia (see appendix 1). Some receptors have a high threshold and are activated only when stimuli may damage the tissue. These are called nociceptors and are peripheral endings of primary sensory neurons whose cell bodies are located in the dorsal root ganglia and trigeminal ganglia. Most nociceptors are free nerve endings. Nociceptors can be found in two different types with different characteristics: the A-delta fibers which are thin and myelinated with a transmission velocity of 5-25 meters/second, and the C-fibers which are even thinner in diameter but not myelinated and therefore achieve a transmission velocity of 0.1-2 meters/second. The A-delta gives rise to a pain that is distinct and easy to locate, whereas the C-fibers give rise to a diffuse pain with an aching character. The different classes of nociceptors are widely distributed in the body and often work together (4).

Nociceptive afferent fibers lead into the dorsal horn of the spinal cord/brain stem. These are subdivided into laminae, which can be described as distinct layers. Each layer has its own characteristics since classes of primary afferent neurons that convey distinct modalities terminate in distinct laminae. Nociceptive neurons are located in the superficial dorsal horn, in the marginal layer (lamina I) and the substantia gelatiosa (lamina II). These neurons receive synaptic input directly from A-delta and C-fibers. In lamina I some neurons respond uniquely to noxious stimuli, the so called nociceptive-specific neurons. Other neurons in the same lamina respond in different degrees to different stimuli, and are thus named wide-dynamic-range neurons. Lamina II is made of interneurons which respond to different kinds of stimuli. Laminae III and IV respond mainly to nonnoxious stimuli. Lamina V consists mainly of wide-dynamic-range neurons, but receive stimuli from visceral structures as well. The convergence of these different input into the same lamina may give an explanation to “referred pain”, i.e. pain from injury to a visceral structure (i.e. myocardial infarction) is displaced to other areas of the body surface (i.e. pain in chest and left arm). Higher centres are unable to discriminate the source of the input correctly since a single projection neuron receives input from both regions. Clinically this gives rise to differential diagnostic problems.

Information about tissue injury is carried from the spinal cord to the brain through five major ascending pathways. The spinothalamic tract is the most prominent pathway and comprises the axons of neurons in laminae I and V-VII. These axons cross the middle line in the spinal cord and terminate in the thalamus. Injury to the spinothalamic tract and its targets causes a severe pain named “central pain”. The spinoreticular tract comprises neurons from laminae VII and VIII. The spinomesencephalic tract comprises neurons from laminae I and V, the cervicothalamic tract from laminae III and IV, and finally the spinohypothalamic tract which arise from neurons from laminae I, V and VIII.

Synaptic transmission between nociceptors and dorsal horn neurons is mediated by chemical neurotransmitters released from sensory nerve endings. The major, and in most detailed studied, excitatory neurotransmitters are glutamate (an amino acid) and substance P (a neuropeptide). These are released from primary afferent terminals and have distinct physiological actions on postsynaptic neurons. Substance P appears to enhance and prolong the effect of glutamate. The range of action between the two classes of transmitters may differ since some of the neuropeptides released from sensory terminals can diffuse quite impressive distances from their site of release. This occurs because there is no specific reuptake mechanism for neuropeptides as there is for the amino acids. Thus, the release of neuropeptides from a single afferent fibre is likely to influence many postsynaptic dorsal horn neurons (5).

2
Mechanisms of neuropathic pain

In recent years, patophysiological mechanisms underlying neuropathic pain after peripheral nerve damage have been distinguished in many aspects (6). NP is caused by disease or injury of the thermonociceptive part of the nervous system, and this injury may be located at any level of the nervous system regardless of etiology. NP is distinguished from other pain conditions where the causes of pain are diseases in the non neural tissues. A significant number of medical conditions and diseases may be the sources of this pain condition. For instance, it may emerge as a result of an autoimmune disease (i.e. multiple sclerosis), metabolic diseases (painful diabetic neuropathy), infections (i.e. shingles and the sequel postherpetic neuralgia, HIV), vascular disease (i.e. stroke), trauma, iatrogenic/treatment caused, and cancer. NP can be classified based on the location where the lesion has taken place, in other words it can be peripheral or central. Central neuropathy accounts for, as the word indicates, nerve lesions in the central nervous system (i.e. spinal cord and brain). On the other hand, peripheral neuropathy includes lesions in the peripheral nerves leading into the spinal cord or brainstem (i.e. trigeminal nerve).

Neuropathic pain is characterized by spontaneous pain/paresthesia/dysesthesia as well as stimulus evoked abnormal sensations such as hyperalgesia, allodynia or non-painful stimulus evoked sensibility aberrations. It can be distinguished from other types of pain by the following inclusion criteria:

- Pain that persists after the healing period is complete.
- Presence of neurological sensory signs that are spontaneous or stimulus provoked i.e pain, paresthesia, dysesthesia, hyperalgesia, allodynia or non painful sensory disorder.
- Presence of other neurological signs, i.e. autonomic signs.

The theoretical detection of NP may seem easy to assess, but in clinical practice it is not that simple, due to several reasons:

- Several diagnostic tests have to be positive for NP to be confirmed
- Pain has a subjective aspect that can not be measured objectively.
- The borderline between different diagnoses is not always clear.
- NP is not a static condition, and may change in intensity and quality in an unpredictable manner over time, and may also become chronic.
- Lack of agreement among scholars and colleagues concerning the definition of NP (6).

Pain Control

The perception of pain is regulated by several modulatory systems within the central nervous system which alter the respons to noxious stimuli. Pain is not simply a direct product of the activity of nociceptive afferent fibers but is regulated by activity in other myelinated afferents that are not directly concerned with the transmission of nociceptive information (5). It is possible to distinguish three principal mechanisms for pain control: 1) concurrent input at segmental level, 2) activation of descending pain control systems and 3) psychological mechanisms (6).

1) Concurrent input at segmental level:
The idea that pain results from the balance of activity in nociceptive and nonnociceptive afferents was formulated in 1965 by Melzack and Wall and is called the gate control theory (4). The gate control theory states that activity in nociceptors can be blocked by simultaneous activity in mechano-receptive nerve fibers in the first relay station in the dorsal horn or
trigeminal nuclei. The effect of this kind of pain inhibition is limited both in extension and magnitude (6). The gate control theory provides a neurophysiological basis for the observation that a vibratory stimulus that selectively activates large-diameter afferents can reduce pain. This hypothesis is the theoretical rationale for the use of TENS (trancutaneous electrical stimulation) for pain relief (5).

2) Activation of descending pain control systems:
Experiments with animals have shown that stimulation of the periaqueductal gray region (PAG) and nucleus raphe magnus (NRM) in the brain produces a profound and remarkably selective analgesia. These areas in the brain consist of groups of neurons which are part of the descending pain control system. From PAG impulses project to medulla oblongata where there are synapses with NRM which in turn lead to different levels in the dorsal horn of the spinal cord. The main transmitter substance in this signaling is serotonin (5HT) (6). In the spinal cord these descending pathways inhibit nociceptive projection neurons through both direct connections and through inter-neurons in the superficial layers of the dorsal horn (5). Pain inhibition takes place when the released transmitter substance in the signaling between PAG/NRM and the dorsal horn binds to its specific receptor. In the descending pain control system there are three types of transmitter substance receptors: aminergic receptors (i.e. for serotonin, noradrenalin), opioid receptors (i.e. for endorphin, encephaline, dynorphine) and GABA receptors (6).

3) Psychological mechanisms:
More than any other sensory modality pain is influenced by emotional state and environmental contingencies. The experience of pain is highly individual which makes it difficult to treat clinically. Furthermore it is extremely dependent on experience and therefore varies from person to person. That a positive care or hypnosis can give pain relief is best explained by activation of the brain which in turn activates PAG and NRM (6).

Mechanisms underlying spontaneous pain
There exist a number of mechanisms that may lead to the development of spontaneous pain as a result of nerve injury. A lesion to trigeminal sensory nerves can lead to increased receptive field size, abnormal discharges of trigeminal central neurons. In addition, neuronal changes can also occur.

Abnormal or increased discharge in the primary afferent nerves can be mediated by both ectopic impulse activity and ephaptic transmission. The increased ectopic activity is believed to be caused by the accumulation of sodium channels along the injured nerve fibre. Spontaneously evoked activity may also arise in the more centrally located nociceptors of the dorsal root ganglions, which may obstruct the effect of a diagnostic blockade by local anaesthetics. This can cause confusion when trying to distinguish peripherally mediated pain from centrally mediated pain.

Ephaptic transmission is described as a communication between nociceptive fibres and spontaneously activated non-nociceptive fibres (i.e. mechano receptive/motor/sympathetic fibres), caused by the destruction of the electric isolation between adjacent nerve fibres. Also, nociceptive nerve fibres that are activated by adjacent neurons display longer periods of activity. Thus, the chain of recurring action potentials results in both spontaneous symptoms and continuous after-sensation caused by one single sensory stimulus.

In addition, demyelination of the nerve fibres may also lead to spontaneous activity with subsequently increased mechanic sensitivity and recurring action potentials even after the stimulus has stopped. This phenomenon is caused by the incorporation of sodium channels (after a nerve injury) into those parts of the neuron that are usually free from any sodium
channels. It is believed that this phenomenon is a probable cause of diabetic neuropathy and compression neuropathy.

After a nerve injury (i.e. peripheral axotomy), a number of neurochemical changes take place rather soon. Among other things, certain peptides usually associated with nociceptive pain decrease in favour of other peptides: Substance P and CGRP levels decrease whereas Vasoactive Inhibitory Peptides (VIP), Galanin (GAL) and Neuropeptide Y (NPY) levels increase. VIP replaces the role of SP as an excitatory neurotransmitter. GAL in turn expresses a partial inhibitory effect on nociceptive pain.

There exists also a long time known relation between pain and the sympathetic nervous system. It has been summarised under the concept of sympathetically mediated pain (SMP) and it stipulates that some pain conditions can be maintained by the sympathetic system. Sympathetic agents tend to cause increased pain, whereas administration of their antagonists has the opposite effect. In fact, the relieving effect of administering local anaesthetics into the stellate ganglion is just another diagnostic tool which supports the relation between pain and the sympathetic nervous system. In addition it has been shown that following a peripheral nerve injury efferent sympathetic nerve fibres grow into the ganglion. Under normal conditions, when no lesion on the peripheral nerves has occurred, this phenomenon does not occur. The coupling of these newly grown nerve fibres with dorsal root neurons has been observed in cases with allodynia.

Following a section of a peripheral nerve sprouting of the nerve takes place, which results in nerve terminals ending in more superficial layers the of dorsal horn. This could partly explain certain types of alldynia, because the reorganization of fibres may connect terminals of A-beta fibres to nociceptive neurons. In addition, changes in segmental inhibitory segments may occur at the V and spinal dorsal horn levels. For instance, large amounts of excitatory amino acids are released. These induce NMDA receptors intensively, and thus cause destruction of inhibitory interneurons, which have a central part in the inhibition of pain. Therefore, pain impulses can be excited repeatedly.

Another important phenomenon that has a central role in general as well as neuropathic pain is sensitisation. It can be described as simply a facilitated excitability of the injured peripheral nerve and is caused by the release of chemicals from the peripheral tissues or primary afferent nerve endings (peripheral sensitization). The nociceptive component could also last over a longer period of time and cause changes in the subnucleus caudalis or in the spinal region, which would lead to prolonged feeling of pain. This is termed as central sensitization (4, 8).

**Examination Criteria**

Reaching a correct diagnosis is a requirement and a helpful tool for the clinician when determining the appropriate treatment. Therefore, it is of great importance that this step is done systematically and with great care.

First of all, it is required by the clinician to acknowledge the patients chief complaint and gather all relevant information (including assessing general physical and psychosocial status). A comprehensive pain history interview containing patient’s pain complaint, past pain experience, onset of the pain, the symptomatic course of the pain since onset, the treatment’s clinical effects on the pain, type of treatments the patient has undergone for the pain previously. Furthermore, the clinician needs to go into deeper questions about the nature of the pain experienced by the patient by finding information on the intensity of experienced pain, location, referral patterns, character (i.e. dull, aching, throbbing, shooting, burning, shooting, electrical), duration of the pain, frequency, temporal pattern (i.e. continuous, episodic, paroxysmal), exacerbating/relieving factors (i.e. jaw function, exposure to cold, light touch, analgesics, exercise) and associated signs (i.e. tearing, warm sensation, dizziness,
vertigo, tingling, numbness). It may be preferential to hand the patient a list of pain descriptors from which he or she should select and mark the relevant sensory alterations (signs/symptoms). The impact the pain possesses on the patient’s life is also inquired. Altogether, the patient’s shared information plays a crucial role in directing the clinician into the right path of diagnosis. The comprehensive history should, obviously, also contain information on the patient’s general medical history, medications, review of organ systems, dental history as well as personal history.

Once the initial interview with the patient is completed, the clinician proceeds to make a comprehensive physical examination of the orofacial and neck region. Usually this includes visual inspection, manual palpation, auscultation, measurements of mandibular range of motion, probing, and percussion. The physical examination is undertaken both extra orally and intra orally. Whenever neuropathic pain is suspected, this step of the examination contains an extensive and accurate cranial nerve examination by examining the motor (whenever applicable) and sensory aspects of each cranial nerve. Cranial nerve dysfunction is commonly manifested as sensory alterations, specific to the cranial nerves. Sensory alterations may be reported as anesthesia, paresthesia, dysesthesia and even allodynia (17). The dentist should grossly rule in or out serious neurological conditions and in more complex cases refer the patient to the appropriate medical personnel. Furthermore, the physical examination should be filled in with imaging features to confirm the presence of suspected pathology.

Secondly, the clinician needs to analyze and integrate all the data included in the first assessment to reach a weighted conclusion.

In the third step, the pain problem is categorized based on the clinical course (i.e. acute or chronic), temporal features (i.e. persistent and continuous, episodic or transient), location (i.e. extra orally/intra orally, maxilla/mandible, unilateral/bilateral, irradiating), limits (i.e. clearly/diffusely localized), location of source, and associated or not with systemic pathology (8).

Treatment Strategies

The NNT for a certain drug is the number of patients needed to treat to obtain one patient with at least 50% pain relief. A more or less equally important aspect in determining drug efficacy is the potential harmfulness associated with a particular drug. It’s therefore important to determine the number needed to harm (NNH) which is the numbers needed to treat before there is one patient with pronounced or intolerable side effects. Drugs with a low NNT/NNH ratio will generally be superior to drugs with a high NNT/NNH ratio (12).

It is important once again to state that there are no predictors available for therapy choice, and that only about 40% of patients with chronic neuropathic pain can be offered pain relief with current available medication. Given the limited effectiveness of present treatments, combining different drugs may result in improved results at lower doses and with fewer side effects. Although supporting evidence is missing concerning drug combinations, many clinicians use a combination of several drugs as treatment strategy. Future trials are needed to evaluate optimal drug combination and dose ratios as well as safety, compliance and cost-effectiveness (7).

In general one can state that effective pain relief therapy does not exist in the majority of the neuropathic pain cases. For the individual peripheral neuropathic pain case there are no predictors for therapy choice which makes the management a kind of “trial and error” treatment. Complete elimination of pain is rare, and many patients do not respond at all to many of these treatments. A reduction of pain intensity by 30% to 40% should be considered a good response (8).
Some reports suggest first hand choice of treatment to be conservative as in exercise, behavioral therapy, supportive psychotherapy or peripheral sensory activation (i.e. TENS) for activation of the endogenous pain control systems. This treatment strategy has been proved effective in only a fraction of cases, but since there are basically no true adverse effects and the treatment might prove effective, conservative interventions should be regarded as the first hand choice of treatment (4).

Pharmacologically there are a number of groups of drugs that have shown some efficacy regarding pain relief in neuropathic pain, of which the most common are antidepressants, antiepileptic, opioid analgesics, locally acting analgesics, topical agents, NMDA-interacting drugs and miscellaneous drugs.

The first hand pharmacological treatment choice is the group of antidepressant drugs since this is the most extensively studied drug treatment for neuropathic pain and thus has the best documented treatment strategy outcome. Tricyclic antidepressants reduce neuropathic pain according to numerous studies (4, 7). The analgesic effect is most probably due to noradrenalin and serotonin reuptake blockade, NMDA-receptor antagonism and sodium-channel blockade. The antidepressants are also thought to reinforce the effect of the endogenous amines in the body’s own pain control system. Examples of effective antidepressants are amitriptyline, imipramine, nortriptyline and desipramine (4, 7).

Of the anticonvulsants carbamazepine and phenytoin have shown to be the most effective. Both have significant adverse effects and are therefore not the first-line therapy choice, except for treatment of trigeminal neuralgia where carbamazepine can be considered the first hand choice. The effect of carbamazepine is thought to be due to its action as a use-dependent sodium channel blocker and calcium channel antagonist. The mode of action of phenoitoin is similar to that of carbamazepine. Numerous papers have described the benefits of the anticonvulsant gabapentin (an alpha-2-delta subunit voltage-gated calcium-channel antagonist) for treating a variety of chronic pain disorders, including peripheral neuropathies. Gabapentin is a structural analogue of GABA and was developed as a GABA agonist. It interacts selectively with subunits of voltage dependent calcium channels to reduce activity. It has demonstrated analgesic efficacy and improvement in sleep and mood in several RCTs. For the anticonvulsants the number of RCTs is very limited but in general one can state that the number of patients responding to this treatment is much less than for the antidepressant group (4, 7, 8).

The role of opioid analgesics in neuropathic pain has been controversial. Among clinicians and scientists there are divided meanings concerning the effect of opioids. Some say that persons with chronic peripheral neuropathic pain are insensitive to opioids, while other suggests that this insensitivity only is relative and that with an increase in dosage, with simultaneous treatment of adverse effects, pain relief is possible. However, a meta-analysis from 2005 suggests that most evidence is beneficial with an, on average, pain reduction of 20%-30% (7). Evidence is thus supporting the longterm efficacy of opioids, for example tramadol or morphine. The main concern with the use of opioids is that patients will become psychologically dependent on the drugs. The risk of drug abuse from prescribing opioids has not been well-quantified in long –term prospective trials, but most pain experts believe that it is low in patients with no history of addiction (4, 7, 8).

Locally acting analgesics are interesting since they cause minimal systemic side effects thanks to the local application. An example being the lidocain patch 5% which has been shown to relieve localized pain in post-herpetic neuralgia with no increase in side effects (NNT=4). The use of intraoral topical medications is related to some practical inconveniency though. The topical agent has to have mucosal adhesive properties, if not it will be very easily washed away from the area of application. Since these products still are relatively new in the market several strategies are being employed to overcome this problem. An example of this
kind of medication is Orabase B, an anesthetic used in the mouth to relieve pain and irritation with the active painkilling ingredient benzocaine. Another topical agent which recently has made its way into the treatment options list of neuropathic pain is capsaicin, an ingredient of hot peppers. Persistent application of capsaicin will desensitize a chronic peripheral neuropathy thus offering pain relief. Intraoral application is made possible by fabricating an acrylic stent to cover the affected area when applying a capsaicin-mixture. Capsaicin causes an unpleasant burning sensation for several days before desensitization occurs, so the treating clinician should be fully aware of this before treatment commences. Capsaicin has demonstrated significant analgesia in a number of RCTs (4, 7, 9, 10).

The NMDA-receptor has been considered a potential target for modulating chronic pain in view of the fact that it’s known to have a role in long-term potentiation and central sensitization. Extensive work in animal models has suggested that inhibitors of the NMDA glutamate receptor reduce hyperalgesia in neuropathic pain and other pain states. Ketamine and dextromethorphan are both agents with NMDA-antagonist activity and they have shown effective in smaller RCTs. Unfortunately available agents have limited efficacy since they produce intolerable side effects, such as sedation, ataxia, hallucinations, nightmares, delusions, unusual reactions and schizophrenic psychosis (7, 8, 9).

Experiments are being made to find new agents to relieve neuropathic pain; here we will only briefly review some. Mexiletine, an oral antiarrythmica agent and sodium channel blocker, has been studied in several controlled trials with inconsistent results since it proved to be superior to placebo in 2 of 7 RCTs (12). Mexiletine is the oral analogue of lidocain, and more convenient since it can be dosed orally. Clonidine, an alpha-2-agonist sympathetic blocker has showed efficacy in some patients with diabetic peripheral neuropathy and post herpetic neuralgia. Cannabinoids have been found to play a role in experimental pain modulation, and there is growing evidence of their efficacy in managing neuropathic pain. An oromucosal spray containing a mixture of tetrahydrocannabinol and cannabidiol proved modest benefit in a RCT of neuropathic pain following brachial plexus avulsion. Adenosine is an endogenous substance which is found in all cells in the human body. Recently published studies have shown that IV administrated adenosine gives pain relief and reduces alldynia in patients with peripheral neuropathic pain (4, 8, 12).

Materials and Methods
The purpose of this project was to perform a retrospective study of peripheral trigeminal neuropathy in a dental/orofacial pain population. The scope of the project thus included examination criteria, the formation of a differential diagnosis list, a discussion of the classification of trigeminal neuropathic pain, the pathophysiology of neuropathic pain, the treatment modalities and treatment outcomes.

The source of patient information was received from a database of unnamed neuropathic pain patients from the Orofacial Pain Clinic in UCLA. The database provides information on patients who have been diagnosed and treated for chronic peripheral trigeminal neuropathy. In addition, we aimed to give a detailed presentation on the diagnosis and treatment modalities (i.e. medications, topical agents, centrally active medications, plastic stents, etc) for peripheral neuropathy, as well as the treatment outcome/results (based on patients’ subjective information, using the Visual Analogue Scale).

Database
The database provided to us by the Orofacial Pain Clinic at UCLA includes the following variables:
1. Gender and age of 53 patients treated at the clinic for neurogenic or neuropathic pain. No names were disclosed.
2. Patients’ description of the pain they experience.
2. Neuropathic Diagnostic assessment by clinicians at the Orofacial Pain Clinic.
Type of Oral and Topical medication prescribed to the patient.
3. Patient’s response to various treatment modalities: to given oral medications, topical medications (if at all prescribed) in order of usage. That is, only one medication at a time was given to the patient.
4. Psychological assessment of patients, based on the Minnesota Multiphasic Personality Inventory (MMPI), Beck Depression Inventory (BDI) and BDI.
5. Patient’s evaluation of their pain after treatment, using the Visual Analogue Scale (VAS).

Results
Due to missing information from the patient database we are unable to present the effect of the given medications in a statistically significant manner. Therefore, we decided to present a number of patient cases. The relevant cases are presented below. For an explanation to the psychological tests see appendix 3. For an explanation to the given medications see appendix 4. When several medications are given it is the last one that has proved positive effect. This is true for oral and topical medications separately.

Patient case 1:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: Male, 56 years old
Cause of pain: Unknown
Patient’s pain description: Burning, sharp, aching
Blockable: Not done
Positive provocation tests: Static allodynia, dynamic allodynia
Topical medication use: Capsaicin, Orabase B
Oral medication use: None
Positive result: Not done
VAS, first visit: 58
Psychological tests: BDI 9, BAI 28

Patient case 2:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: Female, 66 years old
Cause of pain: Trauma
Patient’s pain description: Aching, throbbing
Blockable: Partial
Positive Provocation tests: None
Topical medication use: Capsaicin, Orabase B, Carbamazepine, Neurontin
Oral medication use: Lyrica, Desipramine
Positive result: Not Done
VAS, first visit: Not done
VAS, second visit: 46
VAS, third visit: 57
VAS, fourth visit: 85
VAS, fifth visit: 85
Patient case 3:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: Female, 53 years old
Cause of pain: Unknown
Patient’s pain description: Aching, shooting, stabbing
Blockable: Not done
Positive provocation tests: Static allodynia, dynamic allodynia
Topical medication use: Capsaicin, Orabase B, Carbamazepine
Oral medication use: Neurontin
Positive result: Yes
VAS, first visit: 51
VAS, second visit: 0
VAS, third visit: 32
VAS, fourth visit: 57
VAS, fifth visit: 0
Psychological tests: MMPIL 47, MMPIF 65, MMPIK 37, MMPI1 69, MMPI2 59, MMPI3 61, MMPI4 79, MMPI5 57, MMPI6 74, MMPI7 66, MMPI8 67, MMPI9 62, MMPI10 51.

Patient case 4:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: Female, 68 years old
Cause of pain: Trauma
Patient’s pain description: Aching, burning, shooting
Blockable: Yes
Positive provocation tests: Dynamic allodynia
Topical medication use: Orabase B
Oral medication use: Neurontin
Positive result: Yes
VAS, first visit: 63
VAS, second visit: 29
VAS, third visit: 7
VAS, fourth visit: 3
VAS, fifth visit: 4
Psychological tests: BDI 11

Patient case 5:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: Female, 47 years old
Cause of pain: Trauma
Patient’s pain description: Aching, throbbing
Blockable: Yes
Positive provocation tests: None
Topical medication use: Orabase B, Capsaicin
Oral medication use: Neurontin, Lyrica, Flexeril
Positive Result: Yes
VAS, first visit: 57
VAS, second visit: 18
VAS, third visit: 3
Psychological tests: BDI 11, BAI 4

Patient case 6:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: male, 51 years old
Cause of pain: Surgery
Patient’s pain description: Aching, sharp, stabbing
Blockable: Yes
Positive Provocation tests: Static allodynia
Topical medication use: Orabase B, Neurontin, Ketamine
Oral medication use: Neurontin, Lamictal
Positive result: Yes
VAS, first visit: 81
VAS, second visit: 88
Psychological tests: BDI 40, BAI 45

Patient case 7:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: Female, 36 years old
Cause of pain: Trauma
Patient’s pain description: Aching
Blockable: Yes
Positive provocation tests: None
Topical medication use: Orabase B, Capsaicin
Oral medication use: Neurontin, Baclofen
Positive result: Yes
VAS, first visit: 70
VAS, second visit: 44
VAS, third visit: 44
Psychological tests: BDI 24, BAI 15

Patient case 8:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: Female, 69 years old
Cause of pain: Endodontics
Patient’s pain description: Aching, throbbing, sharp
Blockable: Not Done
Positive provocation tests: Dynamic allodynia
Topical medication use: None
Oral medication use: Trileptal
Positive result: Yes
VAS, first visit: 49
VAS, second visit: 0
VAS, third visit: 0
VAS, fourth visit: 0
Psychological tests: BDI 2, BAI 14

Patient case 9:
Diagnose: Peripheral Trigeminal Neuralgia
Sex and age: Female, 65 years old
Cause of pain: Unknown
Patient’s pain description: Aching, throbbing, sharp
Blockable: Yes
Positive provocation tests: Dynamic allodynia
Topical medication use: None
Oral medication use: Neurontin, Carbamazepine, Baclofen
Positive result: Yes
VAS, first visit: 1
VAS, second visit: 10
VAS, third visit: 8
VAS, fourth visit: 3
VAS, fifth visit: 2
Psychological tests: Not Done

Discussion

Material
The material we aimed at using as the base for this project showed to miss some important information. Many of the variables were missing for each one of the patients, for example VAS and psychological tests. This could be due to lack of calibration among the clinicians or loss of information when transferring from the patient’s file to the database. Due to missing information we were unable to make a statistically supported assessment on the effect of the different topical and oral medications. This is not a gigantic problem to overcome and if the clinicians involved only calibrate their investigation methods further, and more care is given when transferring data from patient files to the database, these problems of missing information should easily be overcome.

Further, a significant number of the patients listed were diagnosed with central neuropathic pain disorders and we had to limit ourselves to only 9 patient cases out of totally 53, not only since our aim was to investigate peripheral neuropathic pain conditions but also because 8 additional peripheral patient cases were too incomplete to be incorporated at all. We were at the beginning of the project unaware of this very important fact, and had we known, the problem formulation would have been modulated to fit the available material better.

However this list is being updated continuously and is far from complete at this stage. It is a very useful tool of guidance in the jungle of medications used for the treatment of orofacial disorders.

Antidepressants
There is a large number of RCTs with evidence of a beneficial effect of antidepressants in neuropathic pain, especially for postherpetic neuralgia and painful diabetic neuropathy. Tricyclic antidepressants and sodium channel blockers are currently considered to be the first-line drug treatments of choice for neuropathic pain. Not only because they are effective in pain reduction, but following logically, also because clinically significant depression is commonly co morbid with pain. It is also a fact that some types of pain can cause depression even in patients with no prior personal or family history of depression. Pain can influence the onset of depression, its recovery, or its recurrence in every phase of depression treatment. If pain is not well managed, only a partial response to depression treatment may be obtained,
and it is therefore important to treat both the pain and the depression together. The data from several controlled studies indicate that tricyclics are effective for both steady and lancinating or brief pains whereas it is more difficult to judge if these drugs also relieve touch-evoked pain. The omnipresent problem in these studies as well as the patient data presented above is that none address the issue of an effect on different pain types, but only show that patients with the different types of pain are relieved of pain in general (12, 15). Out of the nine patient cases presented, one was given Desipramine, a tricyclic antidepressant. However, the VAS showed no improvement or pain relief.

**Anticonvulsants**

Carbamazepine is widely used as anticonvulsant, but also the treatment of choice for trigeminal neuralgia. By blocking sodium channels unspecifically and therefore reducing neuronal excitability in sensitized C-nociceptors it demonstrates membrane-stabilizing properties. In painful diabetic neuropathy carbamazepine has an NNT of 3.3 (2-9.4). It has been reported that it causes a reduction in pain intensity, a reduction in pain paroxysms and in triggers (12).

Gabapentin is a second-generation anticonvulsant with an unknown mechanism of action. Recently published data from a study of a neuropathic rat model suggest that the symptom reducing effect of gabapentin on neuropathic pain is due to inhibition of glutamate release in the spinal cord dorsal horn. Gabapentin have fewer side effects than many of the first-generation anticonvulsants, and it has no significant drug interactions. Gabapentin is recommended as a treatment for postherpetic neuralgia. Baclofen is a GABA-B receptor antagonist which has been examined in trigeminal neuralgia and demonstrated significant pain relief. The NNT for a considerable decrease in painful paroxysms was 1.4 (1.0-2.6) (12, 15).

From our material the majority of the patients, seven out of nine, were given anticonvulsants or muscle relaxants. All seven reported pain relief. VAS decreased in six of the cases.

**Opioids**

Evidence is now compiling that opioids are effective in treating certain types of neuropathic pain. Intravenous infusion of morphine relieves postherpetic neuralgia and it was recently shown that infusion of fentanyl, which is another opioid receptor antagonist, relieves different types of neuropathic pain states. The biggest problems with the opioids are the long list of adverse effects among which nausea, vomiting, respiratory depression, somnolence and neuroendocrine effects can be found. There is also possible to detect a hesitation among primary care doctors against prescribing opioids due to the addictive nature of the drugs. However, available evidence supports the use of long-acting oral opioid analgesics and tramadol for the treatment of certain types of neuropathic pain (12, 15).

None of the nine patients were given opioids, a possible explanation is the controversy concerning possible side effects.

**Locally acting analgesics**

Capsaicin applied on the oral mucosa for 15 minutes in healthy subjects causes moderate levels of pain and heat hyperalgesia, and has been proposed as a pain-provocation test for intraoral pain conditions. As mentioned earlier persistent application of capsaicin will desensitize a chronic peripheral neuropathy. The mechanism of action is not yet completely explored but clinical and animal research has showed that local application offer selective analgesia. A proposed explanation is that capsaicin empties the accumulated substance P in primary afferent C-fibers and also prevents future build up. Topically applied capsaicin cream showed a significant pain relief in 3 of 5 studies in diabetic neuropathy with a combined NNT
of 5.9 (3.8-13). Positive outcome, which is measured as a decrease in VAS pain rating, in post herpetic neuralgia and pain after injury could also be detected with NNTs of 5.3 and 3.5, respectively after topical application of capsaicin. In general, topical treatments for neuropathic pain have a minimal risk of systemic adverse effects and drug-drug interactions. Both capsaicin and lidocain patches are according to the literature recommended for the treatment of post herpetic neuralgia, although the available evidence of efficacy is stronger for the lidocain patch, and its easier to use (12, 13, 14, 15). Of the nine patient cases presented above five were given topical applicable capsaicin. It is next to impossible to evaluate the effect of capsaicin alone in these patient cases since it always was given in combination with other oral drugs. It is therefore not possible to evaluate the effect of the topical medication alone, but one can conclude that the topical medication in combination with another oral drug offered pain relief in 5 of these 9 patient cases. Although this treatment has few side effects besides the burning pain on application at treatment start, it may be less convenient in many patients, since it has to be applied 4 times daily on the entire painful area.

NMDA-antagonists
Ketamine is a drug with NMDA antagonistic effect. Intravenous infusion of ketamine in studies with a double-blind, placebo controlled design have shown an immediate effect in patients with chronic neuropathic pain. Ketamine administrated orally for a few months has been tried in single patients with neuropathic pain and the results are rewarding, but controlled trials have not been published. Experimental and recent small clinical trials have shown that touch-evoked pain or pain responses can be reduced by NMDA receptor antagonists with known action on central hyperexcitability (12).

One patient was given topically applied Ketamine, and reported positive results.

Cannabinoids
Extensive preclinical research has showed analgesic effects of exogenous cannabinoids as well as an endogenous cannabinoid system involved in pain and analgesia. The need for a greater variety of effective therapeutic options has led to heightened interest in evaluating smoked cannabis as a treatment for chronic therapeutic pain, for instance in Canada. Systemic cannabinoids are effective in animal models of acute mechanical and thermal pain, inflammation and hyperalgesia, and nerve injury. In healthy human volunteers, smoked cannabis increased pressure pain tolerance thresholds. A RCT from 2007 showed that smoking cannabis cigarettes three times a day reduced HIV-SN (HIV-associated sensory neuropathy) pain by 34% compared to 17% with placebo cigarettes. As mentioned earlier a >30% reduction in pain is considered a clinically significant level of improvement. In the study previously mentioned the NNT on the primary outcome measure of >30% pain reduction among all completing patients was 3.6. Further, two recent placebo-controlled studies of cannabinoids for central neuropathic pain associated with multiple sclerosis produced results similar to the above mentioned RCT (11). It is a controversial subject to use cannabis as pain relief and even more it is not legal in a majority of the world’s countries, but perhaps one should consider alternative treatments in experimenting with pain relief since it obviously is so difficult to diagnose and treat.

Concluding discussion
Despite the increasing number of trials of different drugs in different neuropathic pain conditions, it is still only the efficacy of tricyclic antidepressants in painful polyneuropathy and postherpetic neuralgia that relies on a sufficiently large total number of patients studied. Future studies on the effect of different drugs on different neuropathic pain phenomena may unmask pain mechanisms and guide choice of treatment for single patients. None of the new
treatments appear to be more effective than the tricyclics or the older anticonvulsants, according to the amount of RCTs comparing different drug groups, but when comparing the NNT for commonly used medications for neuropathic pain they show similar efficacy (12, 15). The results from different RCTs are thus very confusing and sometimes even contradictory.

Because neuropathic states involve multiple symptoms, often modulated by more than one mechanism, partial effects are to be expected as a result of treatment with a single agent. The use of different agents with different mechanisms, either from the same or different drug classes, may be of substantial benefit to patients with neuropathic pain. The management of neuropathic is well suited to the use of rational polypharmacy (15).

Effective pain treatment requires not only a comprehensive understanding of available therapies, pain mechanisms, and the complex neuropsychology of co morbidities, but also the ability to generate a unique treatment plan for each patient. A doctor must never forget that each patient is very different from the next.

Acknowledgments

The authors wish to thank Dr. Robert Merrill for providing us with the database on neuropathic patients and for giving helpful ideas and assistance throughout the entire project. We would also like to thank Dr. Malin Ernberg for guidance.
References

14. www.fass.se
16. www.drugs.com
18. www.cps.nova.edu/~cpphelp
Appendix 1

- Allodynia- a painful response to a non-painful stimulus.
- Anesthesia- general or local insensitivity, as to pain and other sensation.
- Central sensitization- following a peripheral tissue damage or inflammation nociceptive neurons may become sensitized due to repetitive depolarisation caused by an increased release of certain neurotransmitter.
- Dysesthesia- an unpleasant abnormal sensation, whether spontaneous or evoked.
- Hyperalgesia- an increased painful response to a normally painful stimulus.
- Neuropathic pain- pain initiated or caused by a primary lesion or dysfunction in the nervous system.
- Paresthesia- an abnormal sensation, whether spontaneous or evoked (not describes as unpleasant).
- Referred pain- pain from injury to a visceral structure is displaced to other areas of the body surface
- Secondary hyperalgesia- pain sensitivity that occurs in surrounding undamaged tissues (9).
Appendix 2

Cranial nerve examinations

- I: Olfactory nerve: Smell lost or disturbed.
- II: Optic: Recent changes in far, near, or peripheral vision.
- III, IV, V: Oculomotor, Trochlear, and Abducens: Pupillary asymmetry; double vision; ocular paralysis.
- V: Trigeminal nerve: Numbness or loss of tactile sensation in the Orofacial area; decrease in strength of masticatory muscles; Response to pin prick is tested in all three divisions of the trigeminal nerve on one side and compared to the response in the same distribution on the contra lateral side. The response to light touch is tested in the same manner. Trigeminal motor is tested by having the patient clench their teeth while palpating the masseter muscles bilaterally. The muscle response should be approximately equal bilaterally.
- VII: Facial: Taste disturbances; facial paralysis.
- X: Vagus: Voice hoarseness; asymmetric retraction of the soft palate.
- XI: Accessory: Decrease in strength of shoulder elevator muscles and rotational muscles of the head.
- XII: Hypoglossal: Lateral deviation of the tongue during protrusion (9).
Appendix 3

Psychological Assessment tests

Minnesota Multiphasic Personality Inventory (MMPI):
This is designed as an objective test for the assessment of psychopathology. It consists of 550 statements to which the patient has to respond. The inventory is then scored in subunits. Eight of these subunits are classified as clinical scales: Scale 1- Hypochondriasis, Scale 2- Depression, Scale 3- Hysteria, Scale 4- Psychopathic deviate, Scale 6- Paranoia, Scale 7- Psychastenia, Scale 8- Schizophrenia, Scale 9- Hypomania, Other scales include Scale 5- Masculinity/Femininity, Scale 0- Social introversion. Three supplemental measures were developed to display the validity of the clinical profile given by the clinical scales: The L (Lie)-scale, containing 25 statements; The F (infrequency) scale, containing 64 statements; and eventually the K scale. The MMPI is being used for screening, assessment, selection, and prediction applications in both research and clinical settings.

Beck Anxiety Inventory (BAI):
This test is designed to discriminate anxiety from depression. It consists of 21 items. The items describe a common symptom of anxiety, and the patient is supposed to rate how much he or she has been bothered by each symptom over the past week. Each item is given a score between 0 and 3 based on how much the patient is bothered by the symptom. The scores are eventually summed and the maximum score possible is 63.

Beck Depression Inventory (BDI):
This test measures the presence and degree of depression in adults and Adolescents. It consists of 21 items, each of which assess typical symptoms or attitudes that are present during depression (18).
Appendix 4

Type of medication used for the patient cases presented:

- Baclofen- Antiepileptic medication.
- Capsaicin- Local analgesic.
- Carbamazepine- Antiepileptic medication.
- Desipramine- Tricyclic antidepressant.
- Flexeril- Tricyclic muscle relaxant.
- Ketamine- NMDA-antagonist.
- Lamictal- Antiepileptic medication.
- Lyrica- Antiepileptic medication.
- Neurontin- Antiepileptic medication.
- Orabase B- Anesthetics.
- Trileptal- Antiepileptic medication (14, 16).