PAIN PATHWAY

LIBRARY DISSERTATION

Submitted to the Department of Conservative Dentistry and Endodontics in partial fulfillment of requirements for the Degree of

MASTER OF DENTAL SURGERY (MDS)
IN
CONSERVATIVE DENTISTRY AND ENDODONTICS

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CERTIFICATE

This is to certify that the Library Dissertation titled "Pain Pathway" a work done by Dr. Jimmy George K, postgraduate student, in partial fulfillment of requirements for the degree of Master of Dental surgery in the subject of ***Conservative dentistry and Endodontics*** *under my guidance and supervision.*

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Dr Jimmy George K

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INTRODUCTION

Pain is a sensory modality that is an unpleasant and emotional experience. Painful sensation is subjective and is biologically useful. It is necessary for survival, being a warning sign and the response of damaged tissue in the body. Pain in the facial area is the most common reason which causes patients to visit a dentist. Orofacial pain is pain associated with the hard and soft tissues of the head, face and oral cavity. There are diverse and several mechanisms related to this pathology. Therefore, orofacial pain physiology should be elucidated and applied to clinical practice in the future.[1]

Pain symptoms often challenge the clinician's diagnostic acumen for it is well known that a correct diagnosis implies correct treatment. Generally, pain is conceptualized as a psychobiologic phenomenon which has two components: perception of pain, which is influenced by anaesthesia and reaction to pain, e.g., fear, anxiety, anguish, depression, or crying, which is influenced by drugs and emotions. The emotional status varies from patient to patient and the disturbances at times can exaggerate the perception of pain.[2]

Despite several advances in the fields of diagnosis, material sciences and therapeutics, oral diseases continue to burden millions of people worldwide, causing a significant impact on health, costs and quality of life. According to the Global Burden of Disease Study 2016, it was estimated that more than 3.5 billion people worldwide suffer from oral diseases with 2.4 billion of those cases being due to dental caries.

Furthermore, it was estimated that 743 million people were affected by periodontal disease, a chronic progressive weakening of the supporting structure of the tooth that led to tooth loss and dysfunction. Despite the fact that oral disease displayed a wide variety of other symptoms, many patients sought dental advice due to the presence of pain in the mouth and/or facial region. Therefore, the diagnosis and management of orofacial pain is an essential need for dentists to ensure the wellbeing of patients, as well as to determine the most appropriate treatment plan for each clinical situation[3].

DEFINITION OF PAIN

In Greek, the word pain means penalty. Plato said that pain arose from within the body, indicating that pain was more of an emotional experience. In recent times, the concept of pain has evolved from one dimension to a multi-dimensional entity involving sensory, cognitive, motivational and effective qualities. Pain is always subjective and every individual uses this word through their previous experience related to the injury. Over time, various definitions have been given to describe and understand this pain in medical literature[4].

Pain Definitions

Task force on taxonomy of the **International Association for the Study of Pain** (IASP) say that pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

The **North American Nursing Diagnosis Association** defines that pain is a state in which an individual experiences and reports severe discomfort or an uncomfortable sensation; the reporting of pain may be either by direct verbal communication or by encoded descriptors.

Medical dictionary by Farlex: Pain is defined as an unpleasant feeling that is conveyed to the brain by sensory neurons. The discomfort signals actual or potential injury to the body. However, pain is more than a sensation or the physical awareness of pain; it also includes perception, the subjective interpretation of the discomfort. Perception gives information on the pain's location, intensity and something about its nature. The various conscious and unconscious responses to both sensation and perception, including the emotional response, add further definition to the overall concept of pain.

Fields et al. "Pain is an unpleasant sensation localized to a part of the body. It is often described in terms of a penetrating or tissue-destructive process (e.g.: Stabbing, burning, twisting, tearing, and squeezing) and/or of a bodily or emotional reaction (e.g.: Terrifying, nauseating, and sickening)."

Monheim: "An unpleasant emotional experience usually initiated by noxious stimulus and transmitted over a specialized neural network to the central nervous system where it is interpreted as such."

Bell: The subject's conscious perception of modulated nociceptive impulses that generate an unpleasant sensory and emotional experiences associated with actual or potential tissue damage or described in terms of such damage.

McCaffery and Pasero offered a clinically useful definition: "Pain is whatever the experiencing person says it does". [4]

BASIC PAIN BIOLOGY

PERIPHERAL NERVOUS SYSTEM

Most often pain is caused by tissue damage, or the potential for tissue damage, and is transmitted via terminal nerve fibers known as primary afferent nerve fibers to higher centres. Two major classes of nociceptive (or pain-sensing) primary afferent nerve fibers can detect potentially damaging noxious stimuli: the A-delta and C fibers. Both fiber types have a wide distribution throughout the body including the dental pulp. In addition, separate class of nerve fibers exist that are involved in detecting non- noxious stimuli such as vibration and proprioception. Such fibers can be found in the periodontal ligament, skin, and oral mucosa and include the A-beta fibers[5].

PRIMARY AFFERENT NEURONS

In the peripheral nervous system, neurons or nerves are referred to as primary afferent (i.e., sensory) fibers. The primary afferent fibers can be divided broadly into A-beta fibers, which transmit light touch or proprioceptive information, and A-delta and C fibers, which encode pain. The tooth is richly innervated by afferent nerve fibers, which are believed to primarily transmit pain in response to thermal, mechanical or chemical stimuli. The vast majority of dental nerves are C fibers that innervate the central pulp, most of which terminate beneath the odontoblasts[6].

A-BETA FIBERS

Rapidly conducting myelinated neurons that respond to light touch are called A-beta fibers. Under normal conditions, activation of the A-beta fibers by high-intensity stimulation results in low-frequency output in the central nervous system. Activation of A-beta fibers normally is interpreted as non-painful mechanical stimulation or "pre-pain" [6]. A-beta fibers have been shown to undergo phenotypic changes that allow them to encode painful stimuli under inflammatory conditions [6].

A-DELTA FIBERS

A-delta fibers are lightly myelinated, have a faster conduction velocity than C fibers and are believed to transmit a sharp or pricking sensation. A-delta fibers respond primarily to noxious mechanical stimuli rather than to chemical or thermal stimuli. Other A-delta fibers may be polymodal (responding to mechanical, chemical, and thermal stimuli)[7] or respond only to cold or mechanical or hot noxious stimuli[8]. In the dental pulp, A-delta fibers cross the odontoblastic layer and terminate in the dentinal tubules[5]. Due to their location and their sensitivity to mechanical stimulation, A-delta fibers are believed to respond to stimuli that result in movement of fluid within the dentinal tubules (e.g., osmotic, mechanical probing, or thermal stimuli applied to the external surface of the tooth)[5]. Consistent with that theory of dentinal pain is the fact that the stimuli causing dentinal fluid movement results in sharp pain associated with A-delta fiber activation. When intense noxious stimuli activate the A-delta fibers, the input to the central nervous system consists of high frequency action potentials.

C FIBERS

C fibers are unmyelinated, have slower conduction velocity, and are associated with a dull, aching, or burning sensation. Most C fibers respond to mechanical, thermal, and chemical stimuli. Because of the difference in conduction velocities, A-delta fibers are believed to transmit early shooting pain, while C fibers transmit late, dull pain. Noxious stimuli that exceed the receptor threshold of these nociceptive primary afferent terminals result in action potentials that travel centrally, signalling tissue damage. In the pulp tissue, the more centrally located C fibers respond to thermal, mechanical, and chemical stimuli and are believed to be sensitized by inflammation[8]. All visceral structures are innervated primarily by afferent fibers conducting nociceptive information such as that carried by A-delta and C fibers.

ALLODYNIA AND HYPERALGESIA

Allodynia and hyperalgesia are two different pain entities characterized by an increased patient response to painful stimuli. In some situations, they can occur shortly after pain stimuli or take some time to develop.

ALLODYNIA

Allodynia is defined as a reduction in pain threshold so that previously non-noxious stimuli are perceived as painful. A classic example is an experience with sunburn. Following sunburn simply wearing a shirt can cause pain. This is an example of a reduced pain threshold (allodynia), resulting in pain from a stimulus that would not normally be painful. If someone gently touches the burned skin, the result may be sudden severe pain. During irreversible pulpitis simply touching a tooth or exerting pressure on it may be enough to provoke pain. Allodynia focuses on a reduced pain threshold. This is an example of increased pain perception (hyperalgesia) caused by a stimulus that would not normally be painful[5].

HYPERALGESIA

Hyperalgesia may be defined as an increase in the perceived magnitude of a painful stimulus. The focus in this condition is on the disproportionate reaction to a stimulus. If a patient has pulp/periapical pathosis, they may experience severe pain from gentle tapping a tooth with pericementitis. This is an example of both a reduced pain threshold (allodynia) and an increased pain perception (hyperalgesia.) Clinicians often rely on clinical testing and the patient's symptoms to detect the presence of hyperalgesia and allodynia. These are important symptoms associated with irreversible pulpitis[5]. Hyperalgesia can be partially accounted for by sensitization of nociceptors (primary hyperalgesia) and by central nervous system mechanisms (secondary hyperalgesia). In the absence of tissue damage, activation of C or A-delta fibers produce transient pain. This pain is believed to serve as a physiological warning. When there is tissue injury, afferent fibers may be activated by lower-intensity stimuli than usual, and the quality of pain may be more persistent and intense. This phenomenon is due, in part, to sensitization of nociceptors, including an increase in spontaneous activity. At the site of tissue injury, there are several inflammatory mediators that can directly or indirectly sensitize primary afferent nociceptors. These inflammatory mediators may be released from the local tissue cells, circulating and resident immune cells, vasculature and endothelial smooth muscle cells, and peripheral nervous system cells[5].

CENTRAL SENSITIZATION

After peripheral tissue injury there is an afferent barrage from C fibers resulting from peripheral tissue inflammation, decreased afferent thresholds, and spontaneous firing of afferent fibers. When a second-order neuron receives a prolonged barrage of nociceptive input, the second-order neuron may also become sensitized. This results in a phenomenon referred to as central sensitization. The result of central sensitization is enhanced processing (i.e., amplification) of neural impulses that are being transmitted to higher brain centres. Two effects of central sensitization are secondary hyperalgesia and referred pain[5]. Secondary hyperalgesia is an increased response to painful stimulation at the site of pain resulting from central nervous system changes. This is in contrast to primary hyperalgesia, which is a lowered pain threshold resulting from sensitization of peripheral neurons. Secondary hyperalgesia might be felt in superficial (e.g., gingiva or skin) or deep structures (e.g., muscles or teeth).

PERIPHERAL SENSITIZATION

After tissue insult there is an inflammatory reaction that often causes pain. The severity of pain that follows is related to several aspects of the injury. Important are the type, extent, and location of the injury; the innervation of the tissue; and the phase of the inflammation. In the nociceptive system, tissue injury can manifest itself as increased responsiveness and/or reduced thresholds to a noxious stimulus, referred to as hyperalgesia[5].

NON-ODONTOGENIC PAIN

Pain of Sinus and/or Nasal Mucosal Origin

Non-odontogenic toothache of sinus or nasal mucosal origin may be due to viral, bacterial, or allergic rhinitis and may be expressed as referred pain in the maxillae or maxillary teeth experienced by the patient as toothache. Bacteria-induced sinusitis pain is often characterized as severe, throbbing pain with a sense of pressure[9].

After a tentative diagnosis of pain due to sinus involvement, it is prudent to refer the patient to a physician for confirmation of the diagnosis and treatment.

Clinical Tips Findings associated with diagnosis of pain due to sinusitis:

- An important diagnostic finding is that more than one tooth may be sensitive to thermal testing and percussion.
- Teeth test is vital in the suspect quadrant.
- Maxillary premolars and molars are most commonly affected by sinusitis.
- Discomfort may be bilateral.
- Typically, pain and pressure increase as the patient's head is lowered between their knees.
- Maxillary local anaesthesia may provide partial relief of pain.
- Sinusitis may be associated with seasonal allergies or upper respiratory infections.
- An antihistamine may provide relief of pain if the cause is sinusitis.
- Reduction of pain after intranasal application of a 4 % lidocaine spray has been reported and is considered diagnostic.

Myofascial Pain

Patients often describe myofascial pain as deep, dull, and aching, and it can be associated with referred dental pain. It has been demonstrated that three masticatory muscles commonly refer pain to teeth. The muscles are the superior belly of the masseter (to the maxillary posterior teeth), inferior belly of the masseter (to

mandibular posterior teeth), the temporal (to maxillary anterior or posterior teeth), and the mandibular to the mandibular anterior teeth[9].

Headache Disorders

Of most interest to dental clinicians are the primary headache disorders, which comprise the bulk of these disorders, and may present as non-odontogenic toothaches. They can be grouped as migraine, tension headache, and cluster headache.

Migraine

Patients may report a history of migraine headaches. This is useful information and leads the clinician to a process of differential diagnosis directed at differentiating pulp/periapical pain from headache pain. Symptoms such as an aura, nausea, vomiting, and photophobia or phonophobia are indicators of non-endodontic pain. Migraine is a common headache, which about 18% females and 6% males experience[10]. It is associated with significant amount of disability, which is the motivating factor that brings the patient to seek care and the reason why this type of headache is the one most often seen in medical clinics.

Migraine has been reported to present as toothache and is likely the most common neurovascular disorder to do so. In addition to this, people with migraine headaches are thought of as having increased regional pain sensitivity that has diagnostic and treatment implications for the clinician.

Migraine headaches typically last between 4 and 72 h. They tend to be unilateral in presentation and pulsatile in quality, with a moderate to severe intensity of pain. Patients may also experience nausea and/or vomiting, as well as photophobia or phonophobia, which are different from toothache. The headache is usually aggravated with routine physical activity, such as walking up stairs.

Caffeine/ergotamine compounds have been used widely in the past as abortive agents for migraine headaches, but in contemporary times they have been replaced with triptans, such as sumatriptan and rizatriptan. Migraine headaches may partially or fully

abate with the use of nonsteroidal anti-inflammatory medications in a similar fashion as toothaches[10].

Tension Headache

Tension-type headache is the most frequent headache disorder experienced, with a range of reported prevalence from 41 to 96 %. The wide range can be attributed to varied definitions of tension headache. Tension-type headaches may be a heterogeneous group of similarly presenting headaches that have overlapping pathophysiologic mechanisms, which has led some researchers to consider aspects of tension-type headache to be the same as musculoskeletal orofacial pain, known as temporomandibular disorders (TMDs)[9].

Cluster Headache

Cluster headaches and other TACs (trigeminal autonomic cephalgias) are rare neurovascular painful disorders that are unilateral and defined by the concurrent presentation of at least one ipsilateral autonomic symptom such as nasal congestion, rhinorrhoea, lacrimation, eyelid oedema, periorbital swelling, facial erythema, ptosis, or miosis that occurs with the pain. The major distinguishing features between these headache disorders are the duration and frequency of the pain episodes, as well as the gender most often afflicted. Cluster headache is the most common of the group, occurring in men three to four times more often than in women, with pain episodes lasting between 15 min and 2 hours, that occur at a frequency of eight episodes per day to one every other day. These headaches occur in clusters, with active periods of 2 weeks to 3 months[10].

From a non-odontogenic perspective, cluster headache and almost all the other TACs have been reported to present as non-odontogenic toothache. The concurrent autonomic features, such as discolouration or swelling in the anterior maxilla, might compound the diagnostic problem by suggesting tooth abscess. Neurovascular headaches tend to be episodic with complete remission between episodes, while odontogenic pain usually has at least some background pain that stays between exacerbations. Local anaesthetic is unpredictable in these cases and can mislead the clinician. Initial management by dentists is aimed at determining whether or not the

pain is of odontogenic origin. If it is not of odontogenic origin, the patient should then be referred to an appropriate care provider.

Neuralgia

The term "neuralgia" when used generically to describe intraoral pain can lead to confusion. The word neuralgia may be used to refer to what is thought of as classic trigeminal neuralgia or tic douloureux. The term "neuralgia" may be used to describe pain felt along a specific peripheral nerve distribution, such as with postherpetic neuralgia and occipital neuralgia, as opposed to a focus of pain disorders that have similar characteristics and are thought to have common underlying pathophysiologic mechanisms[10].

Trigeminal neuralgia is characteristically an intense, sharp shooting pain that is most often unilateral. There is usually an area that, on stimulation such as light touch, elicits sharp shooting pain. The area that elicits the pain is referred to as a trigger zone, and it can be in the distribution of the resultant pain or in a different distribution—but is always ipsilateral. Most patients present with a characteristic trigger zone, but not all patients will present with these finding[10].

An important characteristic of trigger zones is that the response to the stimulus is not proportional to the intensity of the stimulus. That is, slight pressure on a trigger zone results in severe pain. In addition, once triggered, pain typically subsides within a few minutes until triggered again. This is in contrast to odontogenic pain, which may come and go but does not do so in such a predictable and repeatable manner. The trigger for odontogenic pain is an area that has no sensory abnormalities (e.g., dysesthesia or paraesthesia)[10].

As symptoms can be quite severe, patients may insist on treatment even though the clinical findings do not support an odontogenic etiology. The misleading symptoms, along with the willingness of the patient to consent to endodontic treatment, emphasize the importance of a thorough history and clinical evaluation.

Clinical Tips

• Sharp shooting pain in the absence of a dental etiology associated with the symptoms (e.g., caries, large restorations, dental trauma, or recent dental treatment) should alert the clinician to consider trigeminal neuralgia in the differential diagnosis.

• These patients should be referred to a neurologist or orofacial pain specialist in order to confirm the diagnosis.

Herpes Zoster (Shingles)

Ninety percent of the US population has serologic evidence of varicella infection and is at risk for the development of herpes zoster. Approximately one in three people will develop zoster during their lifetime resulting in approximately one million episodes in the United States annually[10].

Neuritis is a condition caused by inflammation of a nerve or nerves secondary to injury or infection of viral or bacterial etiology. In general, pain from a virally induced neuritis, such as recurrent herpes simplex or herpes zoster, is associated with skin or mucosal lesions. Neuritic pain typically is a persistent, non-pulsatile burning and is often associated with sensory aberrations such as paresthesia, dysesthesia, or anesthesia. The pain can vary in intensity, but when stimulated, the pain provoked is disproportionate to the stimulus[10].

As neuritic disorders are caused by reactivation of a virus that has been dormant in the trigeminal ganglion, they are considered projected pain with distribution within the dermatomes innervated by the affected peripheral nerves. In some cases, there may not be cutaneous lesions because the nerves affected by the virus may supply deeper tissues[10].

Localized traumatic injury can also induce neuritis. This injury can be chemical, thermal, or mechanical in nature. A classic endodontic example of a chemical injury to a nerve is the overextension of a highly neurotoxic paraformaldehyde-containing paste (e.g., Sargenti paste) onto the inferior alveolar nerve. Chemical trauma can be due to certain toxic components of the endodontic filling materials such as eugenol, irrigating

solutions such as sodium hypochlorite, or intra-canal medicaments such as formocresol.

Mechanical compression in addition to thermal trauma may be a factor when thermoplasticized material, or carrier-based material, result in overextension of the filling. Mechanical nerve trauma is more commonly associated with oral surgery procedures such as orthognathic surgery and third molar extraction.

Neuropathy

The term neuropathy describes localized, sustained non-episodic pain secondary to an injury or change in a neural structure. Atypical facial pain is included in this category. This term suggests pain that is felt in a branch of the trigeminal nerve and that does not fit any other pain category. If a misdiagnosis occurs a tooth may unnecessarily be extracted. Unfortunately, if the pain is non-odontogenic in origin, the pain will persist and it is then referred to as phantom tooth pain. A limitation in the use of the terms "atypical facial pain" and "phantom tooth pain" is that they suggest that there is pain of unknown etiology, and there is a lack of information regarding their pathophysiology[11].

Psychogenic Toothache

A patient may complain of dental pain (a somatic complaint) without an actual cause. This situation is included in a category of psychogenic toothache that is a psychological disorder. Psychogenic toothache falls within a group of mental disorders known as somatoform. The word "somatoform" is derived from the fact that while the patient has somatic complaints, there is a lack of physical cause. These patients lack a physical cause for pain but will complain of pain but with no local tissue changes. Patients with somatoform disorder are not fabricating the symptoms, nor are they seeking conscious benefit. It is important to make a distinction between somatoform disorders and factitious or malingering disorders[11].

Psychogenic pain may be caused by severe psychological stress. These pains present a general departure from the characteristics of any other pain condition. That is, they may not fit normal anatomic distributions or physiological patterns. The pain may be felt in multiple teeth, and the pain may jump from one tooth to another. The intensity

of pain tends to be more severe than is reflected by the patient's level of concern about their condition. Their response to therapy is variable, including a lack of response or an unusual or expected response. Early identification of psychogenic pain and referral to a psychologist or psychiatrist is necessary to avoid irreversible and unnecessary dental treatment.

Cardiac and Thoracic Structures

Cardiac pain has been cited as the cause of non-odontogenic toothache in a number of case reports. Classically, cardiac pain presents as a crushing substernal pain that most commonly radiates to the left arm, shoulder, neck, and face[11].

Although not as common, anginal pain may present solely as dental pain, generally felt in the lower left jaw. Similar to pain of pulpal origin, cardiac pain can be spontaneous and diffuse with a cyclic pattern that fluctuates in intensity from mild to severe. The pain can also be intermittent, and the patient may be completely asymptomatic at times. The quality of cardiac pain when referred to the mandible is chiefly aching and sometimes pulsatile. Cardiac pain may be spontaneous or increased with physical exertion, emotional upset, or even the ingestion of food. Cardiac pain cannot be aggravated by local provocation of teeth. Anesthetizing the lower jaw or providing dental treatment will not reduce the pain. It can be decreased with rest or a dose of sublingual nitro-glycerine. Diagnosis of cardiac pain, along with immediate referral, is mandatory to avoid impending myocardial infarction[11].

Besides pain of cardiac origin, other chest structures have been reported to produce non-odontogenic toothache. Various cancerous lesions of the lungs have been described to present a mandibular pain, on both the ipsilateral and contralateral sides of the tumour, as well as diaphragmatic pain mediated via the phrenic nerve[11].

LEVELS OF PAIN

In assessing pain, it is useful to have the patient describe the level of pain on a scale of 1–10. A written scale can be used for the patient to self-assess their level of pain. It is helpful in gauging the patient's progress or regression, if the patient must return for an additional diagnostic visit. Some clinicians add descriptors to numbers such as "worst pain imaginable" for number 10 or "barely noticeable" for number 1 and ask the patient to indicate where they fall on that scale.

What Provokes Pain?

It is important to determine what provokes the patient's pain and medications that provide relief. Understanding when the pain started also provides an important diagnostic clue. For example, pain that started years or months ago and remains at a low level does not fit the common profile of endodontic pain. Pulpal pain when initiated usually increases over a relatively short period of time. A vague response to the question of "What brings the pain on?" should raise doubts about odontogenic causation[12].

Non-odontogenic Toothache

Non-odontogenic "toothache" is a less common finding than odontogenic toothache. Differentiating odontogenic from non-odontogenic pain can be a challenging process. There are basic steps that can differentiate the site of where pain is experienced from the actual source of pain. Definitive treatment should never be initiated until the source of pain is clearly identified.

Clinical Tips

An important clue is the absence of pain when the suspect tooth or quadrant is tested with cold, heat, percussion, and palpation. This clue points the inquiry towards a non-odontogenic cause of pain.

The finding of non-odontogenic pain is often confirmed by the patient's description of the onset of pain. If the description omits any of the most common causes of dental pain (e.g., thermal sensitivity or pain during mastication), it is another important clue

pointing toward non-odontogenic causation. While the precise cause of pain at that stage remains unknown, it is clear that an endodontic dental cause is unlikely.

Non-odontogenic Toothache of Myofascial Origin

A myofascial source may be the cause of a toothache due to referred pain. Myofascial pain is often described as a deep, dull, aching pain that may be associated with referred pain to a tooth. Finger pressure and palpation of a specific myofascial trigger point may result in both muscle and tooth pain. Further tests are then required to identify the primary cause of pain. Palpation of musculature is an essential part of the diagnostic process. It is not uncommon to find that a patient who has responded normally to sensibility and clinical tests experiences pain on palpation of the musculature[12].

Maxillary Sinusitis

Non-odontogenic toothache of sinus or nasal mucosal origin may be due to viral, bacterial, or allergic rhinitis and may be expressed as referred pain in the maxillae or maxillary teeth experienced by the patient as a toothache. Bacteria-induced sinusitis pain is often characterized as severe, throbbing pain with a sense of pressure.

After a tentative diagnosis of pain due to sinus involvement, it is prudent to refer the patient to a physician for confirmation of the diagnosis and treatment[11].

Clinical Tips

Findings associated with a diagnosis of pain due to sinusitis:

• An important diagnostic finding is that more than one tooth may be sensitive to thermal testing and percussion.

• Teeth test is vital in the suspect quadrant.

• Maxillary premolars and molars are most commonly affected by sinusitis.

• Discomfort may be bilateral.

• Typically, pain and pressure increase as the patient's head is lowered between their knees.

• Maxillary local anaesthesia may provide partial relief of pain.

• Sinusitis may be associated with seasonal allergies or upper respiratory infections.

• An antihistamine may provide relief of pain if the cause is sinusitis.

• Reduction of pain after intranasal application of a 4 % lidocaine spray has been reported and is considered diagnostic.

"Red Flag Words"

The patient's use of specific words to describe their pain is meaningful. Following are words that provide important clues during the differentiation of odontogenic and non-odontogenic pain.

Words Commonly Used to Describe Odontogenic Pain

• Throbbing

• Pulsating

• Dull ache

• Pressure

• Sharp

Words Commonly Used to Describe Non-odontogenic Pain

• Burning

• Tingling

• Electric

• Searing

• Stabbing

Neuropathic Pain

The International Association for the Study of Pain has defined neuropathic pain as "initiated or caused by a primary lesion or dysfunction in the nervous system". Neuropathic pain has its etiology in neural tissue rather than in the structures that it

innervates. Some neuropathic pains present as episodic pain and some are more continuous. Toothache of neuropathic origin can present as either episodic or continuous pain. Episodic neuropathic pain is characterized by sudden bursts of electric-like pain referred to as neuralgia. When this type of paroxysmal pain is felt in a tooth, it can pose a significant diagnostic challenge for the clinician[11].

Clinical Tips

• Trigeminal neuralgia is the most common episodic neuropathic pain felt in the teeth

Characteristics of Odontogenic Pain

• A dental cause of pain may be apparent during examination, e.g., caries, fracture, and defective restoration.

• Significant radiographic findings include caries, extensive restorations, periapical lesions, and a calcified pulp chamber when others appear normal.

• Dental symptoms: thermal sensitivity and pain during mastication or following pressure against a tooth.

• Local anaesthesia relieves pain.

• Unilateral pain.

• Localized pain[12]

Characteristics of Non-odontogenic Pain

• Absence of apparent etiologic dental cause on radiographs or clinical examination.

• Local anaesthesia does not relieve pain.

• Lack of history of specific cause of pain.

• Pain that crosses the midline.

• Pain described as tingling, shooting, and burning.

• Pain not localized.

• Pain associated with headache.

• Palpation of joint or musculature causes pain.

• Pain associated with emotional stress.

• Presence of multiple teeth that have had endodontic treatment in the same quadrant[12]

Dentinal Hypersensitivity

A patient may present with a chief complaint of a sharp pain provoked during tooth brushing or while eating sweets. The patient may also state that he/she can replicate the pain by rubbing a fingernail against a specific area of the tooth. The initial impression might be one of an endodontic problem, but closer examination may indicate that dentinal hypersensitivity may be the cause of the patient's pain. Typical clinical findings include a vital tooth, gingival recession exposing dentin, sensitivity to air, and pain associated with scraping an explorer against the exposed root. There are two theories concerning the cause of the problem. One involves fluid movement through dentinal tubules resulting in the activation of nociceptors in the inner dentin and pulp[13].

In contrast, exposed dentin that is not sensitive most likely has dentinal tubules that are occluded. Substances that occlude dentinal tubules, in sensitive dentin, are used to eliminate or reduce sensitivity. A second hypothesis for dental hypersensitivity is that some substances may diffuse through the dentin and act directly on pulpal nerves. These hypotheses may occur independently or together. A survey of dentists determined that a variety of therapies are used to treat dentinal hypersensitivity. The most successful treatment was found to be fluoride application. Also widely used were glutaraldehyde/HEMA, bonding agents, potassium nitrates, and restorative treatments. The survey also determined that observation, advice regarding tooth brushing, diet, and laser therapy were the least successful. Despite the therapy used some teeth remain extremely sensitive to provoking stimuli. In those cases, devitalization of the tooth is the treatment of last resort[13].

Central Mechanisms of Orofacial Pain

The International Association for the Study of Pain has defined pain as "an unpleasant, sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." This definition includes not only the sensory aspect of pain but also the emotional and interpretive or cognitive aspects of pain. The emotional factors are more significant in chronic than in acute pain and assert a significant influence that usually has to be recognized and addressed to effectively treat the patient who has chronic pain. Often, chronic pain treatment failures can be traced to ignoring the psychologic issues that are affecting the patient's pain condition[14].

The understanding of chronic pain has advanced significantly in the last 10 years. This understanding has led to improved diagnosis and treatment strategies for pain. Until recently, patients who had facial pain that did not fit the existing understanding and taxonomy were given the diagnosis of "atypical facial pain."

The recent IHS Classification of Headache provides a comprehensive classification system for head and neck pain and removed the "atypical facial pain" diagnosis in favour of "persistent idiopathic facial pain." This is an important step in disengaging the less understood facial pain condition from a co-psychosomatic diagnosis that was implied in atypical facial pain[15].

Pain transmission from periphery to central nervous system

Afferent sensory system: C-polymodal nociceptors and A-delta and A-beta fibers

A basic understanding of the peripheral and CNS is necessary to understand pain mechanisms and to understand how central sensitization develops. Most textbooks on pain discuss dorsal horn mechanisms when referring to the CNS. For orofacial pain, the trigeminal correlate of the dorsal horn is the trigeminal nucleus within the pontine brain stem. Peripherally, the trigeminal nerve provides sensory input from the anterior part of the head, including the intraoral structures. As the nociceptive endings of pain fibers lack specialized receptors, they are named after their afferent fibers and the stimulus that activates them.

The sensory fibers are divided into A-beta mechanoreceptors and three types of nociceptors: A-delta fibers, C–polymodal nociceptors (C-PMNs), and silent or sleeping nociceptors, which are unmyelinated or thinly myelinated. The A-b fibers that respond to light-touch mechano-stimulation are large diameter, fast conducting, and myelinated.

No matter what the frequency or intensity of the stimulus is, these fibers normally encode only low frequency, non-noxious stimuli that are interpreted as light touch[16]. After trauma, the A-beta fibers may begin to signal pain. The A-delta fibers respond to painful mechanical stimuli with an output in the high-frequency range. This is perceived as sharp or stabbing pain. As the A-delta fibers are myelinated, they convey impulses more rapidly than the C-PMNs (Fig 1).

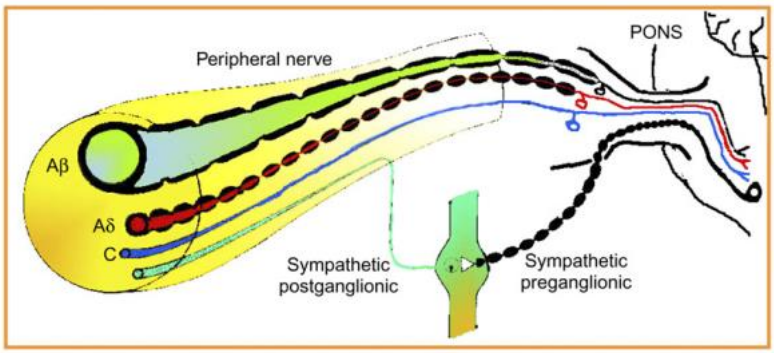

Figure 1- Afferent and efferent fibres

The silent nociceptors are normally mechanically insensitive. They become active when the tissue is injured. These fibers add to the nociceptive input to the CNS[17]. The afferent impulses from all the sensory fibers travel from the periphery through the trigeminal ganglion and trigeminal root, enter the pons, and descends in the trigeminal tract to enter the trigeminal nucleus. Once the fibers have entered the pons, they are in the CNS.

The trigeminal nerve innervates the anterior part of the head. These fibers travel to the trigeminal ganglion and to the trigeminal nucleus in the pons. The trigeminal nucleus is subdivided into three parts: the uppermost subnucleus oralis, the middle subnucleus interpolaris, and the subnucleus caudalis (Fig. 2)[18]. Most of the pain fibers

synapse in the subnucleus caudalis. For pain, the wide dynamic range neurons (WDRs) are the most important second-order neurons in the subnucleus caudalis. They receive convergent sensory input from primary afferent nociceptors and low threshold mechanoreceptors.

Certain features of pain have long puzzled clinicians and researchers. The stimulation of pain from a normally nonpainful stimulus has defied explanation. Conversely, Beecher[19] puzzled over a battlefield phenomenon he noted during the Second World War on Enzio Beach in Italy. Beecher attracted attention to the role of cognitive appraisal with his observations that soldiers wounded during battle complain far less than civilians comparably injured during accidents, presumably because the soldiers were relieved that they had escaped from the battlefield and expected to return home, whereas the civilians evaluated the injury as a threat to comfortable, established lives. Contrasting findings have shown that people who "catastrophize" or self-alarm by focusing negatively upon their distress suffer higher levels of anxiety and are the most disabled and benefit the least from conventional medical care[20]. Patients who have chronic low back pain and are depressed have also been found to misinterpret or distort the nature and significance of their pain. These observations highlight the presence of pain-modulating systems in the body that can turn down or turn up the volume control for pain. This had been implied by Melzack and Wall[21] but was poorly understood when they proposed the Gate Control Theory in 1965.

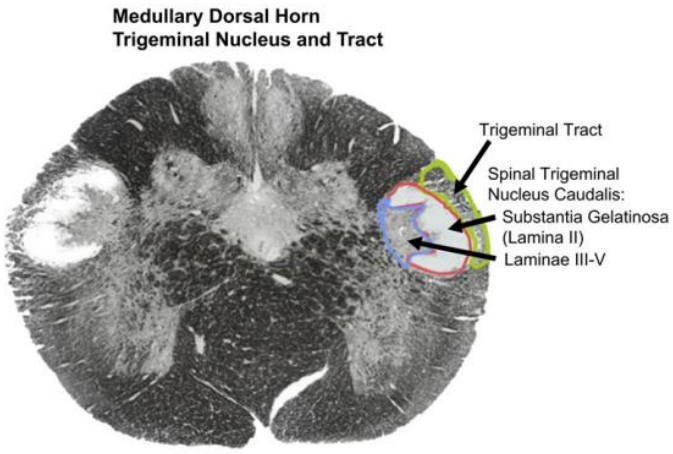

Figure 2 – Trigeminal nucleus caudalis

Second-order neurons

The first interface between the peripheral nociceptors and the CNS occurs in the spinal cord or trigeminal nucleus, the brainstem extension of the spinal cord dorsal horn (Fig. 2). There are many types of receptors and ion channels associated with the cell membrane of the WDR that modulate cell activity. Modulatory circuits can suppress WDR activity and decrease pain or facilitate pain transmission.

The Gate Control Theory and pain modulation

Fig 3 shows the Gate Control of Pain that was proposed by Melzack and Wall in 1962[21] and republished in 1965. Although there have been some modifications to the original theory, most of the system features have been confirmed by research. The Melzack and Wall model describes modulation of pain transmission through the interneuron connections in the substantia gelatinosa. Past research had identified a pain-modulating effect of afferent activity from large-diameter A-beta fibers. The gate control model identified the spinal cord substantia gelatinosa as one of the areas where pain is modulated. Fig. 3 illustrates the modulating effect of the L (light touch fibers) in reducing the effect of afferent activity from the S (c-nociceptors) fibers. Melzack and Wall also theorized that there were descending inhibitory and facilitatory influences, but little was known of these mechanisms in 1965, and it has only been within the last few years that descending inhibitory and facilitatory systems have been identified.

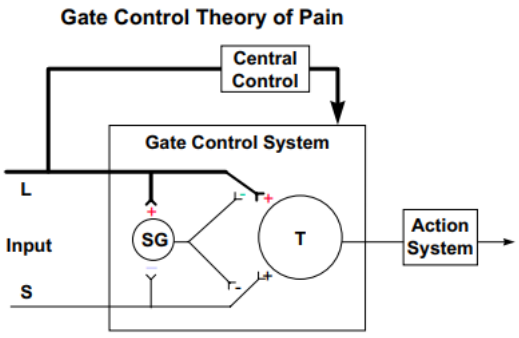

Figure 3 – Gate Control Theory of pain

Central pain processing and central sensitization

The phenomenon of peripheral sensitization develops from an injury induced inflammatory response. Allodynia and hyperalgesia in this model are due to the inflammatory mediators being released at the site of injury. In a tooth extraction site, the inflamed area is marked by increased sensitivity to pressure (static hyperalgesia) that is mediated by sensitized nociceptors. It is expected that this reaction will resolve within a reasonable period of time due to the decreasing activity of the nociceptors and consequent decrease in afferent activity to the dorsal horn.

If the inflammatory process and consequent afferent activity is of sufficient intensity and if there has been neuronal damage, a central process is established that increases sensitization, lowers the threshold of response, and causes ectopic discharges (physiologic changes). Additionally, A-beta fibers begin signalling pain (dynamic mechanical allodynia), and their inhibitory effect is lost (anatomic changes and disinhibition). There is now an increased central release of excitatory mediators, such as glutamate and nitric oxide production (neurochemical changes). These changes stimulate the MAP kinase cascades, resulting in messenger RNA–mediated changes that alter the phenotype of nociceptors and mechanoreceptors such that normal cell response becomes genetically changed to a pathologic state (Fig 4).

Central sensitization is a form of neuroplasticity in which nociceptor activity triggers a prolonged increase in the excitability of dorsal horn neurons. It is initiated by a brief burst of C-fiber activity. The peripheral manifestation of this central process is dynamic hyperalgesia. Torebjork[22] has provided evidence showing that once central sensitization has occurred, A-beta fiber afferents begin to evoke painful response (allodynia)[22]. C-nociceptors have been identified as the primary nociceptor involved in the initiation of central sensitization due to the slow synaptic currents they generate and the low-stimuli repetition rates that cause an increased rate of depolarization in the dorsal horn[23]. This occurs as a result of the activation of ligand-gated ion channels, initially the alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) receptor allowing calcium to enter the cell through the calcium channels. In addition, activation of the metabotropic glutamate and neurokinin receptors by glutamate and substance P causes a G protein–coupled transduction signal that releases calcium from

intracellular stores, further increasing the intracellular calcium levels. This calcium activates a calcium-dependent enzyme system, including protein kinases that phosphorylate the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor at normal resting membrane potentials has a magnesium ion block in the channel, but when the receptor is phosphorylated, the ion is released. Before phosphorylation, the NMDA receptor generates little inward current when glutamate is bound, but after phosphorylation and release of the ion channel block, the NMDA receptor generates inward synaptic currents at normal resting membrane potentials[24]. This process causes increased glutamate sensitivity and is the underlying mechanism that is represented by the expansion of receptive fields and a decrease in the threshold of the dorsal horn neurons.

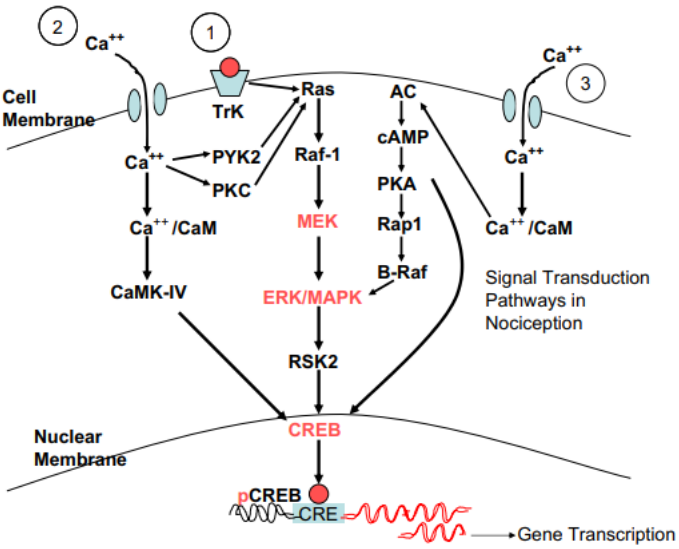

Figure 4 – MAP Kinase Cascade.

Aβ fiber–mediated dynamic hyperalgesia may also be the result of central reorganization of neuronal connections in the dorsal horn. Woolf and others[25] have found that Aβ fibers sprout into dorsal horn lamina I and II after peripheral injury, forming new connections in areas normally occupied only by c-fiber nociceptors. These new connections can apparently signal pain. Additionally, it has been reported that with the neuronal organization and transcriptional changes induced by the sensitization, Aβ fibers begin expressing substance P, previously thought to be

associated only with c-fibers. μ-Opioid receptors are found presynaptically on c-fibers but not on Aβ fibers. Part of the descending inhibitory system uses endogenous opioid action on presynaptic m-opioid receptor. Because these receptors are not found on Aβ fibers, this may account for the relative lack of response to opioid agonists in neuropathic pain.

The influx of calcium through voltage-gated ion channels also occurs on the inhibitory interneurons in lamina II. Calcium may induce excitotoxic cell death, resulting in a loss of inhibitory connections[26]. Mao and colleagues[27] showed that pretreatment with NMDA receptor antagonists seemed to protect the dorsal horn from changes that produced prolonged sensory hypersensitivity. Nitric oxide, arachidonic acid, superoxide, and intracellular calcium overload are the ultimate mediators of neuronal death.

Pain-modulating circuits

Pain is strongly affected by emotions. In the presence of anger, fear, or elation, major injury may be essentially painless. Conversely, in situations associated with dysphoria or when pain is anticipated, subjects often report the occurrence or worsening of pain without additional noxious stimulation. Psychologic factors influence the firing of dorsal horn pain transmission neurons.

It has been observed that stimulation of the periaqueductal gray area in the midbrain increased tail-flick latency in rats when subjected to a painful stimulus. The periaqueductal gray area was demonstrated to be heavily innervated with serotonergic neurons. Subsequently it has been demonstrated that there are connections to the nucleus raphe magnus of the rostral ventral medulla and thence to the nucleus caudalis of the trigeminal nucleus or the dorsal horn of the spinal cord. This system is part of the descending inhibitory system mediated by serotonin. Additionally, a descending system modulated by norepinephrine travels from cortical stimulatory centres to the periaqueductal gray and on to the dorsolateral pontine tegmentum area of the medulla, also connecting to the relay neurons (wide dynamic range) in the nucleus caudalis or dorsal horn. The dorsolateral pontine tegmentum is directly linked to the periaqueductal gray and rostral ventral medulla and projects directly to the

spinal cord dorsal horn and the nucleus caudalis. Pain modulation requires action from both circuits acting in tandem (Fig. 5).

Many of the centrally acting medications used to modulate pain act within these two systems to bring about a reduction of pain that does not involve the opioid system and consequently does not build tolerance to the effects of the medications. One of the most widely used classes of medications for chronic pain is the tricyclic antidepressants. Medications such as amitriptyline and nortriptyline are commonly used for central pain conditions such as postherpetic neuralgia and diabetic neuropathy and work within the serotonin system. Another tricyclic antidepressant, desipramine, works primarily through the norepinephrine system. Their pain inhibitory effects are not linked to the antidepressant effects.

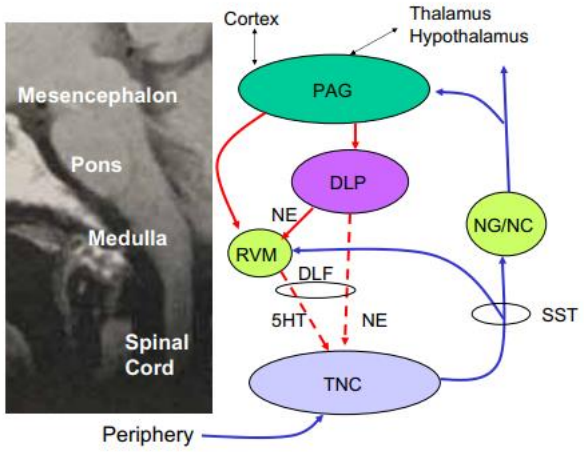

Figure 5 – Pain modulating circuit in dorsal horn

Impact of central sensitization on orofacial pain and temporomandibular disorders

Myofascial pain

Myofascial pain probably represents a neurosensory disorder involving peripheral and centrally sensitized muscle nociceptors. There are many characteristics of the disorder that are best accounted for by equating the pain phenomena with a neurosensory pathophysiology. For example, the primary indication of myofascial pain is the characteristic radiation of the pain from the primary site of palpation to unrelated sites that can be in different dermatomes. This most likely occurs secondarily to central

phenomena, including convergence and activation of adjacent second-order neurons, which would explain the expansion of the receptive field, the lowering of the threshold to stimulation, and the allodynia associated with active trigger points.

Simons proposed a central mechanism for the development of the disorder[28]. He postulated that the muscle nociceptors, when activated by peripheral injury, released substance P, which would diffuse and spread between segments of the spinal cord to activate other adjacent nociceptors and second-order neurons. As we now understand central sensitization, there are many neurotransmitters and ion channels that become involved in the central sensitization process in addition to glial activation (Fig. 6).

The ultimate result is activation of the NMDA receptors on the second-order neurons. When the NMDA receptor is activated, the pain becomes modulated primarily in the CNS and is only partially affected by peripheral mechanisms. In neuropathic pain conditions, NMDA activation connotes a more protracted change in pain. In neuropathic pain, these changes seem to be permanently persistent or at least of long duration. Central sensitization has also been associated with migraine. This situation does not typically have an enduring impact on migraine because the headache tends to resolve within hours. Timely treatment of the migraine can stop the sensitization, and the headache will resolve, or if left untreated, will resolve by itself. Therefore, the sensitization that occurs is of shorter duration. This may be the case with myofascial pain.

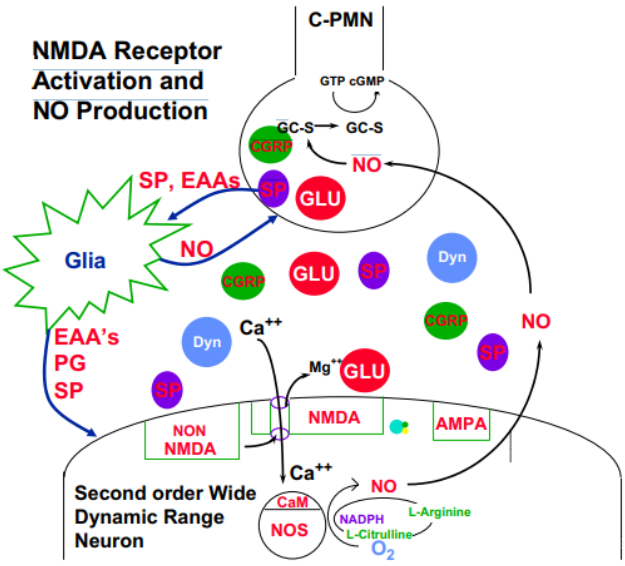

Figure 6 – Glial activation and central sensitization.

Temporomandibular joint pain

Pain of the temporomandibular joint (TMJ) is commonly associated with redness, swelling and allodynia of the skin over the joint. These reactions are modulated by release of peripheral neurotransmitters in the joint space, causing peripheral sensitization. Occasionally, an inflamed joint continues to be painful despite appropriate treatment aimed at decreasing joint inflammation and pain. In some patients, attempting to quell the joint inflammation with intracapsular injections can be met with a significant increase rather than a decrease in pain. This reaction may be seen in patients who have had long-standing TMJ inflammation subsequent to trauma or surgery. This reaction is difficult to manage with traditional conservative TMJ therapy.

The clinician may begin to suspect that a centralized neuropathy has developed in the joint. These joints may not respond to local anaesthetic injections, and, if epinephrine is injected with the local anaesthetic, the pain can become significantly worse, suggesting that sympathetically mediated pain has developed. Often, these patients are recommended to have another surgery to try to correct what is thought to be a musculoskeletal problem but which is a peripheral or central neuropathy. Temporomandibular joints can develop peripheral and centralized neuropathy, and once this occurs, the treatment needs to focus on the types of treatment used in neuropathic pain, such as antiseizure medications, tricyclic antidepressants, narcotics, and sympathetic ganglion blocks to evaluate for sympathetically mediated pain.

Neurovascular disorders

Neurovascular disorders relate primarily to headaches. Until recently, the "science" of headache disorders did not try to equate them with known mechanisms of central neurophysiology. Burstein[29] published several articles in the late 1990s that showed that migraine and other headache disorders were affected by the same central pathophysiology as neuropathic pain. The mechanisms of central sensitization made some of the characteristics of migraine more understandable, such as the lack of response to analgesics and triptans when taken too late in the development of the headache attack. Additionally, the development of central sensitization causes static

and dynamic mechanical allodynia of the head and neck, including the masticatory and cervical muscles. It is not uncommon for a patient to report to an OFP clinician that they get moderate to severe jaw and neck pain with a headache. When a patient is seen during one of these attacks, administration of a triptan or DHE-45 can stop the attack and relieve the jaw and neck pain within minutes. The clinician needs to differentiate between jaw and neck pain due to secondary or central sensitization associated with headache and headache due to painful TMJ and muscle inputs into the CNS that result in headache. In the first case, treating the headache relieves the muscle pain; in the last case, treating the muscle pain can relieve the headache.

Neuropathic pain

Neuropathic pain is commonly seen in the orofacial region. It may develop as a consequence of trauma, simple dental treatment, extractions, endodontic treatment, oral surgery, implants, or orthognathic surgery. The development of a neuropathy does not imply improper or poor treatment. It is not understood why some dental patients develop neuropathies when most do not, even in the face of fairly severe neurotrauma that can occur in everyday general dentistry. Researchers are beginning to suspect that there is a genetic diathesis due to variables such as receptor polymorphism that may predispose someone to develop a neuropathy.[30]

Neuropathic pain in the oral environment due to central sensitization is characterized by chronic aching and burning pain that is persistent over a 24-hour period but which may fluctuate in intensity during this time. The distinguishing characteristic of centralized neuropathic pain is the lack of response to a topical, local, or regional anaesthetic. Neurosensory testing may find that the painful area has pin-prick hyperalgesia and dynamic mechanical allodynia. These neurosensory responses are mediated by central sensitization and A-b fiber stimulation. The classical dental term for this oral neuropathy is "atypical odontalgia".[31.]

Marbach, in the 1990's, suggested that they were phantom tooth pains.[32] Neither of these terms indicate a mechanism behind the pain. In reviewing the characteristics of these two conditions, it becomes apparent that both are describing peripheral and central neuropathies. If the tooth pain is blockable and is characterized by static

mechanical allodynia, it is a chronic peripheral neuropathy. If the tooth pain is not blockable and is characterized by dynamic mechanical allodynia or pinprick hyperalgesia, it is a chronic centralized neuropathy[33]. Treatment of these conditions differ, and it is important to distinguish whether the pain is due to peripheral sensitization or central sensitization.

Peripheral Mechanisms of Odontogenic Pain

Peripheral pain mechanisms associated with odontogenic or temporomandibular disorders and other orofacial pain conditions are generally similar to those seen elsewhere in the body. These similarities include the types of sensory neurons involved and the receptors, channels, and intracellular signalling pathways responsible for the transduction, modulation and propagation of peripheral stimuli. Even though there are some structural features associated with the tooth pulp that make pulpal pain unique, the tooth pulp is considered as a model system to illustrate peripheral pain mechanisms associated with the trigeminal system.[34] This also seems appropriate because toothache is a common presenting symptom for patients seeking dental care.[35] The use of the tooth as a model system for studying pain mechanisms is well established, and advantages include a rich representation of pain fibers and that the stimulation of pulpal nerves produces mostly a pain sensation.[36] In this regard, the tooth as a sensory organ can be considered as a specialized receptor for nociception.

The tooth pulp is composed of connective tissue that is highly vascular and rich in fibroblasts. Within this connective tissue stroma are bundles of axons that provide innervation to the tooth pulp.[37] The distribution and overall pattern of nerve fibers within pulpal tissues have been studied extensively, including in humans and experimental animals. The majority of the axons enter the apex of the tooth, but others may enter accessory foramina when present and ascend the radicular pulp within fiber bundles composed of myelinated and unmyelinated nerve fibers (Fig. 7). Nerve fibers located in these fiber tracts ascend the pulp and terminate as free nerve endings within the pulp or after entering the sub-odontoblastic plexus sequentially along this path.

The sub-odontoblastic plexus is located just inside the odontoblasts and represents a fine network of many small and mostly unmyelinated fibers, many of which originate from thinly myelinated fibers. The sub-odontoblastic plexus (plexus of Raschkow) is extensive and especially elaborate in the region of pulp horns. The odontoblasts outline the entire periphery of the dental pulp and are located at the pulpodentin junction. Many of the unmyelinated nerve fibers located in the subodontoblastic plexus

pass toward and terminate in the odontoblastic layer as free nerve endings, whereas others terminate in the predentin or enter dentin by way of dentinal tubules where they extend to about 100 mm.[38] Although more than 40% of dentinal tubules are innervated in the tip of pulp horns, far fewer tubules are innervated in more apical locations, with less than 1% of tubules innervated in the midradicular region.[39] Stimulation of unmyelinated nerve fibers located in the pulp typically produces a dull throbbing and poorly localized pain sensation, whereas stimulation of the dentin produces a sharp, shooting pain that implicates the activation of more rapidly conducting myelinated fibers.

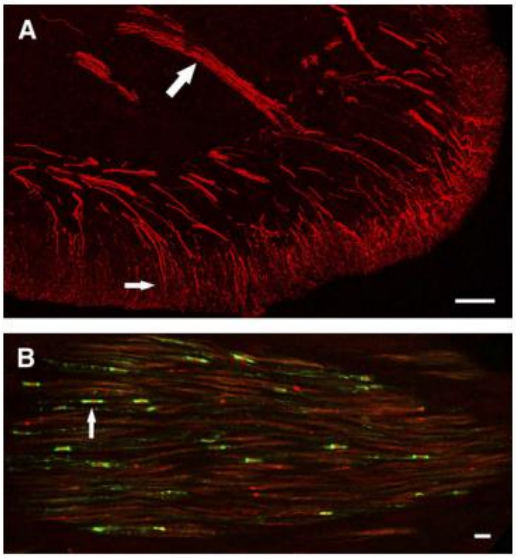

Figure 7 - Confocal micrographs of nerve fibers in the human tooth as identified with the indirect immunofluorescence technique. (A) The coronal aspect of the pulp contains nerve fibers as identified with the neuronal marker PGP9. (B) Nerve fibers located in the radicular pulp contain sodium channels (red) that are prominent at nodes of Ranvier (arrow)

The nerve fiber density within human teeth is quite impressive. A number of ultrastructural studies have evaluated the type (as based on fiber diameter and presence or lack of myelin) and number of axons that innervate anterior and posterior teeth. Comprehensive studies of nerve fibers within posterior teeth are limited to single-rooted premolars. Nair[40] concluded that human premolar teeth contain 2300 axons at the apex; 87% of these are unmyelinated, and the remainder are myelinated. The vast majority of the myelinated fibers are thinly myelinated and fall in the A-delta

class and the remaining 7% represent the more thickly myelinated A-beta nerve fibers. Even though the "average" premolar tooth has a significant nerve density, this can vary depending on the developmental stage and type of tooth[41] and can vary widely among individual samples. The innervation density is also dynamic because it can increase in human teeth with caries.[41] Other axons that enter the tooth pulp originate from postganglionic sympathetic neurons located in the superior cervical ganglion and whose role involves vasoconstriction,[42] whereas parasympathetic fibers may be lacking that provide a vasodilatory role elsewhere.[43] Pulpal vasodilation can be achieved by the release of vasoactive neuropeptides from primary afferent terminals, a process that is integral to the production of neurogenic inflammation.[44] This process most likely involves arterioles because these vessels are most densely innervated in the tooth pulp.[45]

From the perspectives of understanding peripheral pain mechanisms and management, the following section reviews the major classes of receptors and ion channels that confer the ability of nociceptors to "detect" noxious changes in their peripheral area. Fig. 8 summarizes these major classes of receptors and ion channels.

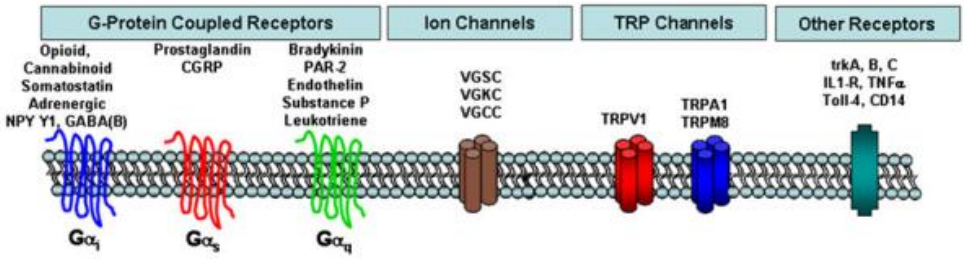

Figure 8 - Cartoon depicting major classes of receptor or ion channels proposed to be present on peripheral terminals of sensory neurons that serve to transduce external stimuli into altered neuronal function.

Mechanisms for detecting stimuli and clinical implications

G-protein–coupled receptors

The G-protein–coupled receptors (GPCRs) comprise a large superfamily of receptors. The GPCR's share a common structure (seven transmembrane regions on the protein) and are called "G-protein–coupled" because they share a common signalling mechanism via activation of a certain class of GTP-binding proteins (aka G-proteins). Thus, the GPCR undergoes a conformational change when a drug or endogenous substance binds to the receptor, resulting in the GPCR binding to a G-protein and initiating a second messenger signalling pathway.[46] Although there are many subtypes of G-proteins and second messenger systems, and the actual signalling pathways are far more complicated than space permits, for our purposes we focus on the three major subtypes of G-proteins: $G\alpha_{i/o}$, $G\alpha_s$, and $G\alpha_q$ and their classic signalling pathways.

GPCR's that are coupled to the $G\alpha_{i/o}$ signalling pathway include opioid, cannabinoid, somatostatin, certain adrenergic subtypes, NPY and GABA (B) receptors. In general, activating a $G\alpha_i$ signalling pathway leads to the inhibition of neuronal function by reducing cAMP levels, opening certain potassium channels (leading to a more negative membrane potential, called "hyperpolarization," and thus reducing the probability of triggering an action potential) and inhibiting certain calcium channels. As a first approximation, drugs that activate the $G\alpha_i$ GPCRs that are expressed on nociceptors would be predicted to be peripherally active analgesics. Drugs that activate peripheral opioid, cannabinoid, adrenergic, Y1, or GABA(B) receptors produce peripheral analgesia or inhibit peripheral neuronal function.[47] Clinicians use several drugs that activate $G\alpha_i$ GPCRs, and many additional drugs are in development as analgesics that act by these mechanisms.

In many respects, the $G\alpha_s$ GPCR's are complimentary to the $G\alpha_i$ family of GPCR's because these receptors typically increase cAMP levels, leading to cellular excitation. Examples of GPCR's that are coupled to the $G\alpha_s$ signalling pathway include prostaglandins and CGRP. Recent molecular studies have demonstrated that of the four known subtypes of prostaglandin receptor, only the EP2 and EP3 subtypes are expressed in trigeminal sensory neurons.[48] Thus, local increases in prostaglandin E2

in dental pulp[49] or periradicular exudates[50] are likely to contribute to odontogenic pain mechanisms via activation of EP2 or EP3 receptors expressed on trigeminal sensory neurons. Although EP receptor antagonists have been developed, the current clinical strategy to control this receptor system is via the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or via glucocorticoid steroids. Both classes of drugs block prostaglandin synthesis by interfering with the function of cyclooxygenase I/II (NSAIDs) or with phospholipase A2 (steroids).

Several GPCR's are coupled to the $G\alpha_q$ signalling pathway, including bradykinin, protease-activated receptors, endothelin, SP and leukotriene receptors. In general, activation of a $G\alpha_q$ – coupled GPCR leads to activation of the phospholipase C/protein kinase C signalling pathways. This can evoke a considerable stimulatory effect on nociceptors, leading to sensitization of the capsaicin receptor, transient receptor potential V1(TRPV1). Recent studies have demonstrated that activation of the phospholipase C signalling pathway can reduce the normally high threshold for activating TRPV1 from temperatures of 43-degree Celsius to as low as 37-degree celcius.[51] This would lead to spontaneous activation of TRPV1 at body temperatures, possibly contributing to the spontaneous pain in patients who have irreversible pulpitis or acute apical periodontitis or other orofacial pain conditions. Prior studies have provided evidence for activation or functional activity of the bradykinin, endothelin, SP, and leukotriene systems in dental pulp.[52]

Voltage-gated ion channels

Voltage-gated ion channels (VGIC's) are transmembrane, pore forming proteins that allow the selective passage of certain ions in a voltage-dependent manner. There are more than 140 members of this superfamily representing one of the largest collections of proteins involved in signal transduction.[53] They also represent key therapeutic targets given their importance in transduction. Within this superfamily are several important classes of ion channels that include the potassium (K^+), calcium (Ca^{2+}), and sodium (Na^+) VGIC's. The activation of these classic channels is a key process involved in the initiation and propagation of action potentials and in the release of neurotransmitters involved in synaptic transmission. Their importance in pain pharmacology is recognized because analgesics exist that function directly on the Na^+

and Ca^{2+} VGIC's, and the actions of many different drugs produce analgesia indirectly through effects on K^+ channels.

Sodium channels: the Na_v s

Much recent interest has been focused on the contribution of altered voltage-gated sodium channel expression to pain states.[54] The importance of sodium channels on pain transmission is well known because the successful practice of "painless" dentistry largely depends on the sodium channel blocking effect of local anaesthetics. Sodium channels are important in action potential initiation and propagation in response to normal stimuli,[55] but they also seem to have a role in increased neuronal excitability and especially spontaneous and ectopic activity associated with inflammatory and neuropathic pain states. The association of altered sodium channel function with basic neuropathic pain mechanisms is strengthened by the relative effectiveness of medications with a sodium channel blocking effect, such as the anticonvulsant carbamazepine in the treatment of neuropathic pain conditions and especially trigeminal neuralgia.[56] The tricyclic antidepressants also represent a useful neuropathic pain medication, and some of their effectiveness may be due to a sodium channel–blocking effect.[57]

Sodium channels are recognized as a diverse group consisting of at least nine different subtypes, or isoforms, localized to nervous system tissues and designated as Na_v 1.1 through 1.9.[58] Although all nine show similarities in structure and as a group show more similarity in function than the Ca^{2+} and K^+ families, some important differences exist. These include a differential nervous system distribution[59] and important differences in expression after inflammatory or axotomy insults.[60] The relative differences in expressions are important physiologically because each sodium channel has unique gating properties that can influence action potential initiation. The isoforms that are normally expressed in sensory neurons include the Na_v 1.1, -1.2, -1.6, -1.7, -1.8, and -1.9 isoforms. The Na_v 1.1, -1.2, and -1.6 isoforms are also found in the CNS, whereas Na_v 1.3 is seen in the developing nervous system.[61] The Na_v 1.6 isoform is the predominant sodium channel located at nodes of Ranvier throughout the nervous system[62] and thus is critically linked to the saltatory conduction of action potentials in myelinated fibers. The Na_v 1.7, -1.8, and -1.9 isoforms are preferentially expressed in

the peripheral nervous system and seen in a subset of nociceptors.[63] Their peripheral nervous system location makes them attractive targets for the development of pharmacologic agents because such agents may lack the CNS side effects associated with many of the current medications that block sodium channels, such as anticonvulsants.

Potassium channels: the voltage-gated potassium channels and others

The potassium-selective channels represent the largest class of ion channels and consist of diverse subtypes. The voltage-gated potassium (K_v) channels are one subtype and represent about 40 of the 70 known potassium-selective channels. Other K^+ selective channels include the inward rectifying, two pore, and Ca^{2+}activated K^+ channels. The Ca^{2+}activated K^+ channels include the big, intermediate, and small conductance K^+ channels.

Each of the K_v genes encodes a single peptide subunit. The active K_v channel is composed of four subunits that can be homo tetramers of the same subunit or hetero tetramers composed of various subunits from within the family. The K_v family members, as designated with the IUPHAR[64] nomenclature and followed by the HUGO Gene Nomenclature Committee nomenclature in parentheses, include K_V1.1–1.8 (KCNA1–7, 10), K_v2.1–2.2 (KCNB1–2), K_v3.1–3.4 (KCNC1–4), K_v4.1–4.3 (KCND1–3), K_v5.1 (KCNF1), K_v6.1–6.4 (KCNG1–4), K_v7.1–7.5 (KCNQ1–5), K_v8.1–8.2 (KCNV1–2), K_v9.1–9.3 (KCNS1–3), K_v10.1–10.2 (KCNH1–2), K_v11.1–11.3 (KCNH2,6,7), and K_v12.1–12.3 (KCNH8,3,4). The K_v 7 family represents the most interesting family from a pharmacologic aspect because mutations in four of the subunits have been associated with diseases such as long QT syndrome, deafness, and seizures. The K_v7.2 to 7.5 subtypes is considered possible targets for the development of anticonvulsants, and, due to the effectiveness of other anticonvulsants in neuropathic pain management, they may also represent pharmacologic targets for pain management. This association seems to hold true because the anticonvulsant retigabine (an opener of the K_v7.2–7.5 subtypes) seems effective in some models of neuropathic and chronic pain.[65] Other K_v subtypes that may be implicated in pain include K_v1.4, which is found in small-diameter dorsal root ganglion neurons,[66] and the K_v4.2 subtype, which is

localized to dorsal horn neurons and when inactivated by extracellular signal-related kinase after injury is inactivated and no longer able to inhibit neuronal firing.[67]

Calcium channels: the voltage gated Ca^{2+} channels and a few others

Activation of the voltage-gated Ca^{2+} (Ca_v) channels have broad-reaching effect on cellular function due to the role of calcium as an important intracellular second messenger system in addition to critical roles in the control of neuronal excitability and the release of neurotransmitters. The structure of the Ca_v is similar to that of the Na_v, consisting of four homologous domains with each domain consisting of a six-transmembrane α-helix segment.[68] The α1 subunit may also be associated with β and α2-δ and -γ subunits, which modify the gating characteristics of the α1 subunit. Currents due to calcium channel activation were initially characterized based on their physiologic properties (L, N P/Q, and R) and then by an alphabetical nomenclature based on that used to classify the K_v.[69] This classification includes Ca_v 1.1 through Ca_v 1.4 (L current), Ca_v 2.1 (P/Q current), Ca_v 2.2 (N current), Ca_v 2.3 (R current), and Ca_v 3.1 through Ca_v 3.3 (T current).

The transient receptor potential channels

The TRP channels represent a family of six different members including some that act broadly in the transduction of sensory stimuli related to pain, temperature, vision, hearing, taste, and pheromone detection.[70] Most are weakly gated by voltage and as a class act as nonselective cation channels that allow the passage of Na^+, sometimes Mg^{2+}, and especially Ca^{2+} into cells. Because Ca^{2+} plays an important role as an intracellular second messenger, they are implicated in the control of many cellular processes, including exocytosis, contraction, apoptosis, migration, cell development, and neuronal excitability. They often work in concert with other receptors, including GCPR's and tyrosine kinases. Tyrosine kinase activates phospholipase C, leading to Ca^{2+} release from the endoplasmic reticulum.[71] The TRP family is somewhat related in structure to the K^+ channels and consists of six transmembrane loops. They can form homomeric functional units or can form associations with other members, allowing the formation of heteromeric units. The six subfamilies of the TRP's include the vanilloid receptor TRPs (TRPV's), the melastatin or long TRP's (TRPM's), the

ankyrin transmembrane protein 1 (ANKTM1 or TRPA1), the classic TRPs, the mucolipins, and the polycystins.[72] Four individual members within these subfamilies (TRPV1, TRPV2, TRPM8, and TRPA1) have been strongly implicated in pain signalling or some aspects of thermoreception, and all allow the passage of Ca^{2+} preferentially more than other cations.[73]

The future: toward a molecular model of pain diagnosis and management

The last few decades have seen a tremendous change in the field of pain. Although the gate control theory of the 1960's emphasized the importance of differences in patterns of afferent input as pivotal in pain perception, contemporary research has focused extensive effort toward understanding the role of receptors and ion channels in the detection of noxious stimuli and in the transmission and processing of this information. This information has two major applications. First, a better understanding of peripheral pain mechanisms contributes to strategies for dental pain control using currently available drugs and the next generation of analgesics. Equally important, knowledge of peripheral pain mechanisms is likely to contribute to our understanding of many chronic pain conditions and supports the development of hypothesis-driven translational clinical research that is likely to increase our understanding of the pathophysiology of many forms of acute and chronic pain.

Although we have focused on the detection of peripheral noxious stimuli and its transmission, it would be overly simplistic to conclude that this is the only important component in pain perception. For example, knowledge of central pain mechanisms, including central sensitization, is equally important in understanding and managing clinical pain conditions. In addition, understanding the affective component of pain and its modulation by psychosocial issues plays an important role in pain control, particularly in chronic pain conditions. Today's skilled clinician must diagnose and treat pain conditions based not on anecdotal lore but on a firm understanding of the biology of pain conditions, the pharmacology of traditional and nontraditional analgesics, and the outcomes from evidence-based clinical trials..

DUAL PATHWAYS FOR TRANSMISSION OF PAIN SIGNALS INTO THE CENTRAL NERVOUS SYSTEM

Even though all pain receptors are free nerve endings, these endings use two separate pathways for transmitting pain signals into the central nervous system. The two pathways mainly correspond to the two types of pain—a fast-sharp pain pathway and a slow-chronic pain pathway.

PERIPHERAL PAIN FIBERS— "FAST" AND "SLOW" FIBERS

The fast-sharp pain signals are elicited by either mechanical or thermal pain stimuli. They are transmitted in the peripheral nerves to the spinal cord by small type Aδ fibers at velocities between 6 and 30 m/sec. Conversely, the slow-chronic type of pain is elicited mostly with the chemical type of pain stimuli but sometimes by persisting mechanical or thermal stimuli. This slow-chronic pain is transmitted to the spinal cord by type C fibers at velocities between 0.5 and 2 m/sec.

As a result of this double system of pain innervation, a sudden painful stimulus often gives a "double" pain sensation: a fast-sharp pain that is transmitted to the brain by the Aδ fiber pathway, followed a second or so later by a slow pain that is transmitted by the C fiber pathway. The sharp pain plays an important role in making the person react immediately to remove himself or herself from the stimulus. The slow pain tends to become greater over time, eventually producing intolerable pain and causing the patient to keep trying to relieve the pain.

On entering the spinal cord from the dorsal spinal roots, the pain fibers terminate on relay neurons in the dorsal horns. Here again, there are two systems for processing the pain signals on their way to the brain.

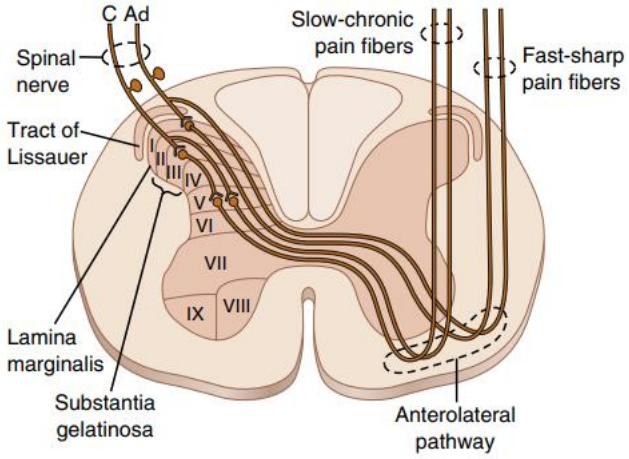

Figure 9 – Transmission of both fast-sharp and slow chronic pain signals into and through the spinal cord.

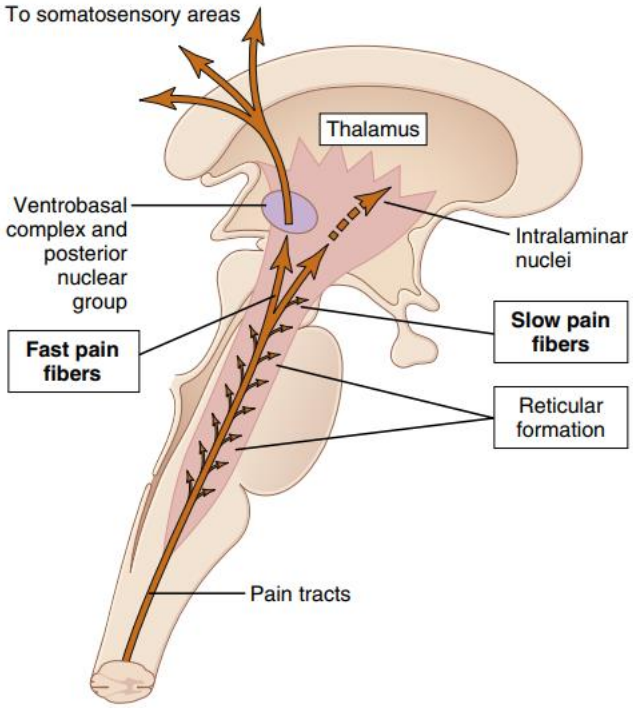

Figure 10 – Transmission of pain signals into brain stem, thalamus, and cerebral cortex via fast pricking pain pathway and slow burning pain pathway.

DUAL PAIN PATHWAYS IN THE CORD AND BRAIN STEM—THE NEOSPINOTHALAMIC TRACT AND THE PALEOSPINOTHALAMIC TRACT

On entering the spinal cord, the pain signals take two pathways to the brain, through (1) the neospinothalamic tract and (2) the paleospinothalamic tract.

Neospinothalamic Tract for Fast Pain

The fast type Aδ pain fibers transmit mainly mechanical and acute thermal pain. They terminate mainly in lamina I (lamina marginalis) of the dorsal horns, as shown in Figure 9, and there they excite the second-order neurons of the neospinothalamic tract. These second-order neurons give rise to long fibers that cross immediately to the opposite side of the cord through the anterior commissure and then turn upward, passing to the brain in the anterolateral columns.

Termination of the Neospinothalamic Tract in the Brain Stem and Thalamus

A few fibers of the neospinothalamic tract terminate in the reticular areas of the brain stem, but most pass all the way to the thalamus without interruption, terminating in the ventrobasal complex along with the dorsal column–medial lemniscal tract for tactile sensations. A few fibers also terminate in the posterior nuclear group of the thalamus. From these thalamic areas, the signals are transmitted to other basal areas of the brain, as well as to the somatosensory cortex.

The Nervous System Can Localize Fast Pain in the Body

The fast-sharp type of pain can be localized much more exactly in the different parts of the body than can slow down chronic pain. However, when only pain receptors are stimulated, without the simultaneous stimulation of tactile receptors, even fast pain may be poorly localized, often only within 10 centimetres or so of the stimulated area. Yet, when tactile receptors that excite the dorsal column–medial lemniscal system are simultaneously stimulated, the localization can be nearly exact.

Glutamate, the Probable Neurotransmitter of the Type Aδ Fast Pain Fibers

It is believed that glutamate is the neurotransmitter substance secreted in the spinal cord at the type Aδ pain nerve fiber endings. Glutamate is one of the most widely used excitatory transmitters in the central nervous system, usually having a duration of action lasting for only a few milliseconds.

Paleospinothalamic Pathway for Transmitting Slow-Chronic Pain

The paleospinothalamic pathway is a much older system and transmits pain mainly from the peripheral slow-chronic type C pain fibers, although it also transmits some signals from type Aδ fibers. In this pathway, the peripheral fibers terminate in the spinal cord almost entirely in laminae II and III of the dorsal horns, which together are called the substantia gelatinosa, as shown by the lateral-most dorsal root type C fiber in Figure 9. Most of the signals then pass through one or more additional short fiber neurons within the dorsal horns before entering mainly lamina V. Here, the last neurons in the series give rise to long axons that mostly join the fibers from the fast pain pathway, passing first through the anterior commissure to the opposite side of the cord and then upward to the brain in the anterolateral pathway.

Substance P, the Probable Slow-Chronic Neurotransmitter of Type C Nerve Endings

Type C pain fiber terminals entering the spinal cord release both glutamate transmitter and substance P transmitter. The glutamate transmitter acts instantaneously and lasts for only a few milliseconds. Substance P is released much more slowly, building up in concentration over a period of seconds or even minutes. In fact, it has been suggested that the "double" pain sensation one feels after a pinprick might result partly from the fact that the glutamate transmitter gives a faster pain sensation, whereas the substance P transmitter gives a more lagging sensation. Regardless of the yet unknown details, it seems clear that glutamate is the neurotransmitter most involved in transmitting fast pain into the central nervous system, and substance P is concerned with slow-chronic pain.

Projection of Paleospinothalamic Pathway (Slow Chronic Pain Signals) Into the Brain Stem and Thalamus

The slow-chronic paleospinothalamic pathway terminates widely in the brain stem, in the large shaded area shown in Figure 10. Only 10% to 25% of the fibers pass all the way to the thalamus. Instead, most terminate in one of three areas: (1) the reticular nuclei of the medulla, pons, and mesencephalon; (2) the tectal area of the mesencephalon deep to the superior and inferior colliculi; or (3) the periaqueductal gray region surrounding the aqueduct of Sylvius. These lower regions of the brain appear to be important for feeling the suffering types of pain. From the brain stem pain areas, multiple short-fiber neurons relay the pain signals upward into the intralaminar and ventrolateral nuclei of the thalamus and into certain portions of the hypothalamus and other basal regions of the brain.

Poor Capability of the Nervous System to Localize Precisely the Source of Pain Transmitted in the Slow Chronic Pathway

Localization of pain transmitted via the paleospinothalamic pathway is imprecise. For example, slow-chronic pain can usually be localized only to a major part of the body, such as to one arm or leg but not to a specific point on the arm or leg. This phenomenon is in keeping with the multisynaptic, diffuse connectivity of this pathway. It explains why patients often have serious difficulty in localizing the source of some chronic types of pain.

Function of the Reticular Formation, Thalamus, and Cerebral Cortex in the Appreciation of Pain

Complete removal of the somatic sensory areas of the cerebral cortex does not prevent pain perception. Therefore, it is likely that pain impulses entering the brain stem reticular formation, the thalamus, and other lower brain centers cause conscious perception of pain. This does not mean that the cerebral cortex has nothing to do with normal pain appreciation; electrical stimulation of cortical somatosensory areas does cause a person to perceive mild pain from about 3% of the points stimulated. However, it is believed that the cortex plays an especially important role in interpreting

pain quality, even though pain perception might be principally the function of lower centers.

Special Capability of Pain Signals to Arouse Overall Brain Excitability

Electrical stimulation in the reticular areas of the brain stem and in the intralaminar nuclei of the thalamus, the areas where the slow-suffering type of pain terminates, has a strong arousal effect on nervous activity throughout the entire brain. These two areas constitute part of the brain's principal arousal system. This explains why it is almost impossible for a person to sleep when in severe pain.

Surgical Interruption of Pain Pathways

When a person has severe and intractable pain (sometimes resulting from rapidly spreading cancer), it is necessary to relieve the pain. To provide pain relief, the pain nervous pathways can be cut at any one of several points. If the pain is in the lower part of the body, a cordotomy in the thoracic region of the spinal cord often relieves the pain for a few weeks to a few months. To perform a cordotomy, the pain-conducting tracts of the spinal cord on the side opposite to the pain are cut in its anterolateral quadrant to interrupt the anterolateral sensory pathway.

A cordotomy is not always successful in relieving pain for two reasons. First, many pain fibers from the upper part of the body do not cross to the opposite side of the spinal cord until they have reached the brain, and the cordotomy does not transect these fibers. Second, pain frequently returns several months later, partly because of sensitization of other pathways that normally are too weak to be effectual (e.g., sparse pathways in the dorsolateral cord).

THEORIES OF PAIN

Several theories have been postulated to describe mechanisms underlying pain perception. The four most influential theories of pain perception include the Specificity, Intensity, Pattern, and Gate Control Theories of Pain.

SPECIFICITY THEORY OF PAIN

The Specificity Theory refers to the presence of dedicated pathways for each somatosensory modality. The fundamental tenet of the Specificity Theory is that each modality has a specific receptor and associated sensory fiber (primary afferent) that is sensitive to one specific stimulus.[73] For instance, the model proposes that non-noxious mechanical stimuli are encoded by low-threshold mechanoreceptors, which are associated with dedicated primary afferents that project to "mechanoreceptive" second-order neurons in the spinal cord or brainstem (depending on the source of the input). These second-order neurons project to "higher" mechanoreceptive areas in the brain. Similarly, noxious stimuli would activate a nociceptor, which would project to higher "pain" centres through a pain fiber. These ideas have been emerging over several millennia but were experimentally tested and formally postulated as a theory in the 19th century by physiologists in Western Europe.

INTENSITY THEORY OF PAIN

An Intensive (or Summation) Theory of Pain (now referred to as the Intensity Theory) has been postulated at several different times throughout history. First, conceptualized in the fourth century BC by Plato in his book Timaeus,[74] the theory defines pain, not as a unique sensory experience but rather, as an emotion that occurs when a stimulus is stronger than usual. Centuries later, Erasmus Darwin reiterated this concept in Zoonomia. One hundred years after Darwin, Wilhelm Erb also suggested that pain occurred in any sensory system when sufficient intensity was reached rather than being a stimulus modality in its own right.[75] Arthur Goldscheider further advanced the Intensity Theory, based on an experiment performed by Bernhard Naunyn in 1859. These experiments showed that repeated tactile stimulation (below the threshold for tactile perception) produced pain in patients with syphilis who had degenerating dorsal

columns. When this stimulus was presented to patients 60 – 600 times per sec, they rapidly developed what they described as unbearable pain. Naunyn reproduced these results in a series of experiments with different types of stimuli, including electrical stimuli. It was concluded that there must be some form of summation that occurs for the subthreshold stimuli to become unbearably painful. Goldscheider suggested a neurophysiological model to describe this summation effect: repeated subthreshold stimulation or suprathreshold hyperintensive stimulation could cause pain. He suggested further that the increased sensory input would converge and summate in the gray matter of the spinal cord. This theory competed with the Specificity Theory of Pain, which was championed by von Frey. However, the theory lost support with Sherrington's evolutionary framework for the Specificity Theory and postulated the existence of sensory receptors that are specialized to respond to noxious stimuli, for which he coined the term "nociceptor".

PATTERN THEORY OF PAIN

In an attempt to overhaul theories of somesthesis (including pain), J. P. Nafe postulated a "quantitative theory of feeling" (1929). This theory ignored findings of specialized nerve endings and many of the observations supporting the specificity and intensive theories of pain. The theory stated that any somaesthetic sensation occurred by a specific and particular pattern of neural firing and that the spatial and temporal profile of firing of the peripheral nerves encoded the stimulus type and intensity. Lele et al. (1954) championed this theory and added that cutaneous sensory nerve fibers, with the exception of those innervating hair cells, are the same. To support this claim, they cited work that had shown that distorting a nerve fiber would cause action potentials to discharge in any nerve fiber, whether encapsulated or not. Furthermore, intense stimulation of any of these nerve fibers would cause the perception of pain.[76]

GATE CONTROL THEORY OF PAIN

In 1965, Ronald Melzack and Charles Patrick (Pat) Wall[77] proposed a theory that would revolutionize pain research: the Gate Control Theory of Pain. The Gate Control Theory recognized the experimental evidence that supported the Specificity and Pattern Theories and provided a model that could explain these seemingly opposed findings.

In a landmark paper, Melzack and Wall (1965) carefully discussed the shortcomings of the Specificity and Pattern Theories—the two dominant theories of the era—and attempted to bridge the gap between these theories with a framework based on the aspects of each theory that had been corroborated by physiological data. Specifically, Melzack and Wall accepted that there are nociceptors (pain fibers) and touch fibers and proposed that that these fibers synapse in two different regions within the dorsal horn of the spinal cord: cells in the substantia gelatinosa and the "transmission" cells. The model proposed that signals produced in primary afferents from stimulation of the skin were transmitted to three regions within the spinal cord: 1) the substantia gelatinosa, 2) the dorsal column, and 3) a group of cells that they called transmission cells. They proposed that the gate in the spinal cord is the substantia gelatinosa in the dorsal horn, which modulates the transmission of sensory information from the primary afferent neurons to transmission cells in the spinal cord. This gating mechanism is controlled by the activity in the large and small fibers. Large-fiber activity inhibits (or closes) the gate, whereas small-fiber activity facilitates (or opens) the gate. Activity from descending fibers that originate in supraspinal regions and project to the dorsal horn could also modulate this gate. When nociceptive information reaches a threshold that exceeds the inhibition elicited, it "opens the gate" and activates pathways that lead to the experience of pain and its related behaviors. Therefore, the Gate Control Theory of Pain provided a neural basis for the findings that supported and in fact helped to reconcile the apparent differences between the Pattern and Specificity Theories of Pain.

The Gate Control Theory is the most promulgated of pain theories and led to some of the most fruitful research in the field of pain. However, many of the details of this theory have been shown to be inaccurate. For example, there were oversimplifications and flaws in the presentation of the neural architecture of the spinal cord, the location and the model pertaining to how large afferent fiber stimulation inhibits or modulates C-fibers,[78] and the hypothesized modulatory system, which we now know includes descending small-fiber projections from the brain stem.[79] Nonetheless, the Gate Control Theory spurred many studies in the field, and this significantly advanced our understanding of pain.

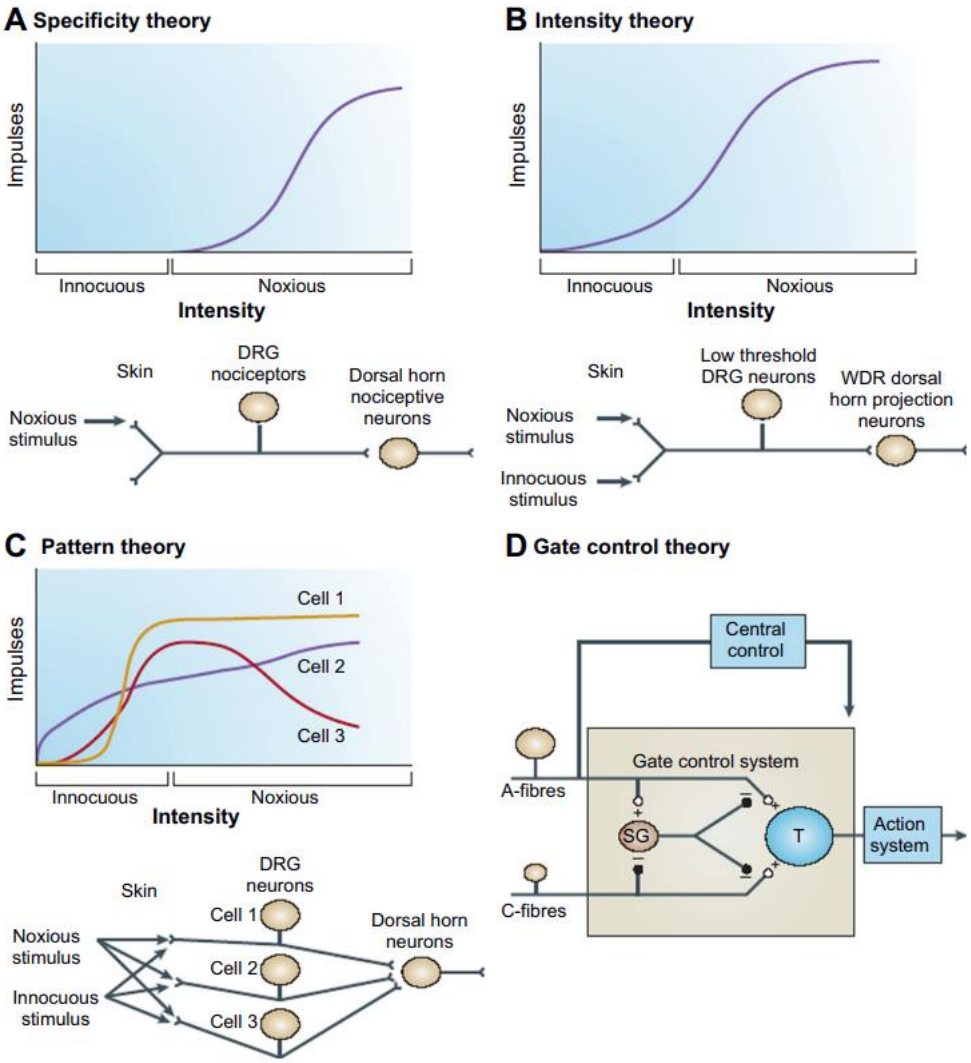

Figure 11- Theories of pain perception.

THE PAINFUL TOOTH: MECHANISMS, PRESENTATION AND DIFFERENTIAL DIAGNOSIS OF ODONTOGENIC PAIN

Applied neurophysiology

Dental afferent nerve fibres, whose cell bodies reside within the trigeminal ganglion, enter the tooth via the apical foramina. Their signals are carried from the pulp via the mandibular and maxillary divisions of the trigeminal nerve to the brainstem where they synapse with second-order neurones in trigeminal nuclei. The fibres cross the midline and ascend to the thalamus where they synapse with third-order neurones which project to higher brain centres. Signals from the majority of afferent nerve fibres within the pulp are perceived as pain.[80] In addition to these afferent fibres, there are also a number of sympathetic efferent fibres which are thought to play a role in haemodynamic control by producing vasoconstriction;[81] parasympathetic fibres are yet to be observed. The periodontium contains numerous mechanoreceptors which contribute to the sensation of pressure and vibration, thus allowing proprioception during mastication;[82] as a result, pain arising from the periodontal tissues is fairly well localised. Conversely the pulp has a paucity of such receptors and thus pain arising from the pulp is poorly localised.

Pulpal nerve fibres are largely of two types: myelinated, fast-conducting A-fibres which are present in the periphery of the pulp and inner dentine along with the odontoblast processes; and the smaller diameter, unmyelinated C-fibres which are more numerous in the body of the pulp and have slower conduction velocities.[83] A-fibres primarily respond to stimuli such as heat, cold, desiccation and direct mechanical stimulation of exposed dentine,[84] and the signals transmitted by these fibres usually produce pain which is rapid in onset and sharp in character.[85] Although a number of A-fibres terminate in the radicular part of the tooth, many more form a dense plexus below the odontoblast layer (plexus of Raschkow), and their endings project some distance into the dentine tubules.[86] Movement of fluid within dentine tubules caused by drying, changes in osmotic pressure and temperature change are thought to produce action potentials in A-fibres innervating the innermost part of the dentine through the activation of mechanosensitive ion channels.[87] Another family of ion channels however

thermo-sensitive transient receptor potential channels (thermo-TRPs) – which are present in dental primary afferent fibres and odontoblasts are now known to contribute to the sensation, and transduction into pain, of hot and cold stimuli.[88] It has been suggested that the experience of pain via exposed dentine may therefore involve both the transduction of mechanical stimuli and direct activation of thermo-TRPs, perhaps involving an interaction of both afferent fibres and odontoblasts.[89] C-fibres are polymodal and respond to intense heat and cold and the presence of inflammatory mediators such as histamine and bradykinin.[90] Stimulation of C-fibres produces a deeper, duller, aching sensation which is poorly localised, and fibres are less responsive to direct mechanical stimulation.

Stimulation of pulp afferent fibres causes the release of several peptides from the neurone such as calcitonin-gene-related peptide (CGRP), substance P and neurokinin A.[91] These substances cause vasodilation within the pulp and the release of inflammatory mediators from pulp fibroblasts, attracting immune cells in a process called neurogenic inflammation.[92] As inflammation proceeds, inflammatory mediators such as histamine, bradykinin, prostaglandins and leukotrienes are released which reduce the thresholds required for nociceptors to generate action potentials; as a result, there is an exaggerated and prolonged response to painful stimuli known as hyperalgesia, and stimuli which would not usually be painful in the healthy tooth produce intense pain – a phenomenon termed allodynia. One mechanism by which this occurs is the sensitisation of thermo-TRPs by various inflammatory mediators, producing thermal hyperalgesia.[93] The voltage-gated sodium channels responsible for initiation and propagation of neuronal action potentials also change during pulpal inflammation; for example, one type of sodium channels involved in pain sensation, Nav1.7, becomes more numerous in the painful pulp, potentially leading to greater sensation of pain.[94] Additionally, nerve fibres sprout new branches, increasing the area from which they receive sensation,[95] and fibres which are usually dormant in the healthy pulp begin transmitting signals. The result of these processes is that nociceptors become more sensitive, and the experience of pain becomes more intense and prolonged – this is termed peripheral sensitisation. In addition, central sensitisation of second and third order neurones occurs in the brain and brainstem,[96]

causing an increased perception of pain and pain spreading over a larger area over time.[97]

Although the A-fibres responsible for pain transmission are classically assumed to be A delta fibre nociceptors, in 2011 Fried, Sessle and Devor proposed the concept of the low-threshold algoneuron.[98] Their reasoning was that light mechanical stimulation (which produces pain in exposed dentine) does not usually result in pain that in other areas of the body, as this does not stimulate the high-threshold A delta and C-fibre nociceptors found in these tissues. To explain this apparent paradox, they proposed the presence of low-threshold mechanoreceptors in the pulp, with conduction velocities in the A beta range. These fibres normally encode the sensation of touch elsewhere and may contribute to the perception of pain in the pulp; this concept appears to be consistent with the evidence, as many pulpal afferent neurones have histological appearances typical of Low threshold mechanoreceptors and express nociceptive neurotransmitters at the level of the trigeminal ganglion.[98]

Pain associated with pulpitis

The term 'pulpitis' describes inflammation of the pulp, and although inflammation may be present without pain,[99] pulpitis is usually painful. The classical regenerate and pulpitis as 'reversible' where symptoms are transient and do not linger, or 'irreversible' where they are persistent or spontaneous[100] is a useful heuristic which is widely used clinically; this clinical distinction does not always match the histological status of the pulp however, or its ability to maintain vitality after treatment.[101] A number of authors have suggested that a proportion of teeth with 'irreversible pulpitis' may have the potential to regenerate, and have suggested the need to reconsider how pulpitis is classified clinically.[102] One proposed classification system favours 'mild pulpitis', where there is a heightened and lengthened response to cold testing but no spontaneous symptoms; 'moderate pulpitis' where symptoms are prolonged and occasionally spontaneous; and 'severe pulpitis' where there is clear spontaneous pain and prolonged pain to warm and cold, with possible pain to percussion and lying down; this system is, however, yet to be clinically validated and widely adopted.

Despite the usual assumption that teeth with 'irreversible pulpitis' require conventional endodontic treatment or extraction, consensus is shifting in favour of minimally invasive endodontics, and vital pulp therapies such as pulpotomy for teeth with symptoms suggestive of inflammation of the coronal pulp, or with deep caries, with the aim of preserving pulpal integrity.[103] Despite this more conservative treatment, some teeth may undergo 'irreversible' degenerative changes requiring conventional endodontic treatment or extraction, and in some cases this may occur without the patient experiencing painful symptoms. The cause of pulpitis in most cases is bacterial invasion arising as a result of caries; however, bacterial ingress may occur during placement of deep restorations, dentoalveolar trauma or secondary to extensive attachment loss in periodontitis, where extra-radicular biofilm may reach the apical area allowing bacteria to enter the pulp via the apical foramina. As caries progresses through the enamel and then into dentine, bacterial byproducts diffuse towards the pulp through dentinal tubules resulting in inflammation of the coronal pulp.[104] There is subsequent increased vascularity, and the activation and sensitisation of A-fibre nociceptors, causing sharp pain on stimulation.

Changes in sodium channel expression and sensitisation of thermos-transient receptor potential channels as discussed may contribute to thermal hyperalgesia at this stage. As caries progresses to include the full width of dentine, bacteria invade the pulp and severe inflammation ensues with areas of necrosis.[105] As inflammation reaches the centre of the pulp, more C-fibres are affected and the spontaneous, intense, lingering pain typical of severe pulpitis develops. Severe pulpitis is more likely to produce C-fibre-mediated pain because these fibres are more tolerant of the tissue hypoxia found in the severely inflamed pulp than A-fibres; C-fibres therefore remain active longer in the degrading tissue. Because of the limited proprioceptive capacity of the pulp and the fact that single afferent nerve fibres may branch to serve multiple teeth, pain associated with pulpitis is typically poorly localised.

Pulpal pain attributed to hypersensitivity

Pulpal pain attributed to hypersensitivity can be defined as pain occurring in association with a clinically normal pulp, and is a diagnosis included in the recently published International Classification of Orofacial Pain (ICOP).[106] Hypersensitivity

occurs due to stimulation of pulpal nociceptors as a result of exposed dentine, for example due to gingival recession, tooth wear or fractures of teeth. The prevalence of hypersensitivity on the basis of clinical examination ranges between 1 and 42% depending on the population studied[107] and is strongly associated with the presence of erosive tooth wear, clinical attachment loss, acid reflux and frequent vomiting.[108] The most commonly accepted mechanism of hypersensitivity is the hydrodynamic theory whereby desiccation of the dentine surface, warm, cold, sweet and mechanical stimuli cause an increased flow of fluid through open dentinal tubules in exposed dentine.[109] This fluid flow generates action potentials in A-fibres within the peripheral pulp and inner dentine by opening mechanosensitive ion channels in these neurones,[110] resulting in sharp, transient pain. Recent evidence has identified the expression of mechanosensitive ion channels and receptors by odontoblasts, which along with evidence supporting signalling between odontoblasts and pulpal neurones suggests that odontoblasts may play a role in pain transduction from dentine stimulation.

Pain from the periapical and periodontal tissue

Periodontal pain is defined in ICOP as 'pain caused by a lesion or disorder involving the periodontium: the periodontal ligament and/or the adjacent alveolar (peri-radicular) bone tissue', and therefore may be caused by a number of conditions. As pulp inflammation progresses in the presence of apically advancing bacterial colonisation, the inflammatory process finds its way into the periapical tissues through apical and lateral foramina.[111] In many cases, apical inflammation may be observed during pulpitis and before necrosis of the pulp. Local inflammation causes tissue destruction and pain, which is well localised due to the numerous mechanoreceptors found in the periodontal tissues. Periapical nociceptors become sensitised by many of the same mechanisms as in pulpitis,[112] and this process may produce pain which is constant and aching in character, with exacerbation of pain on biting due to compression of the periapical tissues. The history may reveal preceding pulpitis pain-like symptoms followed by a relatively painless period due to cessation of nociceptive signals from the pulp where necrosis occurs. Clinical examination may reveal a mobile

tooth due to periodontal destruction, and the tooth will most likely be tender to percussion due to stimulation of periapical nociceptors.

Sensibility testing may either elicit no response in the case of pulp necrosis, or produce pain if sensate, inflamed pulp tissue remains.[113] Depending on the degree of bony destruction, and the speed and duration of the inflammatory process, radiographic signs may range from a normal periapical appearance, widening of the periodontal membrane space, loss of the lamina dura of the alveolus or the appearance of frank periapical radiolucency.[114] Long-standing, chronic lesions are more likely to show radiographic changes compared to more rapidly progressing inflammation, which may show little change in the early stages. Diagnosis is supported by the presence of a well localised, painful tooth with tenderness to percussion, increased mobility, radiographic changes and a painful or absent response to sensibility testing. While the inflammation associated with gingivitis may cause pain and discomfort, periodontitis is usually a painless disease.[115] Acute periodontal conditions such as periodontal abscess may present with well-localised pain due to the abundance of mechanoreceptors in the periodontal tissues, as well as suppuration, bleeding, swelling and tenderness. There may be tenderness to percussion of the tooth and since the pulp is usually unaffected there may be a normal response to sensibility testing (a short-lasting, slightly painful sensation to thermal testing but absence of lingering pain, and appreciable sensation of the same nature on electrical testing). Periodontal abscesses most often occur in patients with pre-existing periodontitis as an exacerbation of their condition. Necrotising periodontal diseases such as necrotising gingivitis and periodontitis present with severe pain, malaise and halitosis, and are characterised by necrosis and ulceration of the periodontal tissues.[116]

Pericoronitis is a common cause of pain, particularly associated with erupting third molar teeth. Diagnosis is usually unchallenging due to the presence of a partially erupted or impacted tooth with traumatised, tender and inflamed mucosa surrounding or overlying it. There may also be trismus and suppuration. Occlusal trauma may be another cause of pain from the periodontal tissues, and presents as pain on biting, potentially in association with increased mobility, tooth migration and widening of the periodontal membrane space on radiographic examination.[117] Occlusal trauma results

from excessive occlusal forces (e.g., parafunctional habits or occlusal discrepancies) in a normal periodontium, or normal/ excessive occlusal forces where there is existing attachment loss. A common example of this is where a newly placed restoration has not been properly contoured, and is 'high' in the occlusion, causing excessive occlusal force and resulting pain. Gingival and periodontal inflammation caused by food impaction beneath defective approximal contacts, fractured teeth or tooth tissue loss due to caries are further sources of pain from the periodontal tissues.

Cracked teeth

Teeth with significant fractures which separate the tooth into independently mobile parts are usually easy to diagnose; however, incomplete fractures (cracks) often precede this, particularly in mandibular molar teeth with extensive restorations (although the situation also often occurs in unrestored teeth).[118] Cracked teeth have long caused much difficulty in diagnosis and management,[119] and patients with such cracks often present with confusing symptoms and findings on examination. This condition can be very difficult to diagnose because cracks may not be visible to the naked eye or may lie beneath otherwise seemingly sound restorations. For example, patients may complain of pain on biting, but the tooth is not tender when percussed with a mirror handle. This is because the periodontal tissues – which are tested by percussion – are not the source of the pain, and as a result the pain is not well localised. Occlusal forces wedge the crack open, and on release of the pressure, rapid movement of fluid in the dentinal tubules which have been exposed by the crack causes sharp pain.[120] Provocation of pain by asking the patient to bite on each cusp in turn using an instrument such as a FracFinder (Directa; Upplands Väsby, Sweden) or Tooth Slooth (Professional Results Inc.; CA, USA) may elicit familiar symptoms.

The tooth may give an entirely normal response to sensibility testing because if the crack does not extend into the pulp, the pulp may not be inflamed. Some patients however report symptoms of pulpal pain which is exacerbated by hot and cold, or spontaneous, lingering pain. In this situation, either bacterial products have diffused into dentinal tubules towards the pulp as a result of bacterial colonisation within the crack or there may be direct exposure of the pulp by the crack; in either case, the pulp becomes inflamed.[121] It is important to identify these cracks and take steps to

prevent their propagation, to prevent progression to more severe pulpitis or terminal fracture of the tooth. Unfortunately, radiographic examination is usually unhelpful in the diagnosis of cracked teeth as the cracks are not well visualised unless they serendipitously run in the direction of the X-Ray beam. One clinical feature that may be present if the crack involves the periodontal ligament is a localised area of increased periodontal probing depth due to attachment loss at the site of the crack; although not always present, this feature represents poorer prognosis for the tooth and indicates microbial presence in the crack. Transillumination may be useful in visualising a crack, as light transmitted through the tooth is blocked by discontinuity of the enamel and dentine and a clear boundary will appear. Dedicated fibre optic light sources exist for this purpose (among others), although light from a dental handpiece or composite curing light (taking care to protect the operator and assistant's eyes) is often effective. Other techniques such as the use of commercially available dyes usually used for caries detection, and magnification using loupes or an operating microscope also aid detection.

DIAGNOSIS

The key to managing pain is an accurate diagnosis. This cannot be reached unless a comprehensive history, careful examination and appropriate special tests and investigations are performed. The history itself is often the key to the diagnosis and the nature of the pain, its timing, duration, location and precipitating factors guide the clinician to the cause. For example, pain in response to change in temperature rather than pressure may indicate a pulpal cause in favour of a periodontal one, and pain on biting might make pain of periodontal origin or a cracked tooth more likely. Similarly, short-lived pain in response to cold drinks may make pulpal pain as a result of mild pulpitis or hypersensitivity more likely than if the pain was spontaneous and lingering, as might be seen as a result of severe pulpitis.

A careful and thorough examination should identify any pathology affecting the teeth which may indicate a source of pain, and efforts should be made to reproduce the patient's pain by palpation, percussion, selective loading of teeth and response to thermal stimuli. Similarly, suspicious teeth should be tested for sensibility using appropriate methods. A provisional diagnosis is often formed following the history and

examination, and radiographic tests serve to confirm or refute this. For example, secondary caries around a deep restoration found on a bitewing radiograph may support a provisional diagnosis of pulpal pain caused by severe pulpitis, and radiolucency around the apex of a tooth which is tender to percussion on examination may confirm a diagnosis of apical periodontitis as the cause of periapical pain.

The results of the history, examination and investigations should never be relied upon in isolation – not infrequently the results of each of these can be at odds with each other, and the picture may not be clear. All of the information obtained should be interpreted in combination to reach an accurate diagnosis. Where the diagnosis is not certain, on occasion it may be appropriate to delay treatment until the picture is clearer, in preference to performing an irreversible procedure. Occasionally, the clinical findings do not tally with the patient's symptoms, and although it may be tempting to try to do something to a tooth which seems otherwise sound when the patient insists it is the cause of their pain, it should always be considered that the cause of the patient's pain may not be odontogenic, and a definite diagnosis should always precede any invasive intervention. It is not unheard of for patients with non-odontogenic pain to have had multiple teeth restored, endodontically treated and extracted by well-meaning dentists with no improvement in their symptoms. Pain arising from a non-odontogenic cause such as temporomandibular disorders, trigeminal neuralgia, post-traumatic trigeminal neuropathic pain and headache disorders including migraine may present similarly to odontogenic pain; this is discussed in depth elsewhere in this issue.

PAIN MANAGEMENT IN ENDODONTICS

Despite many recent advances in technology, the number of people who experience dental pain is relatively high.[122] Many of these people will need root canal treatment to relieve their pain, but such treatment is known to induce high levels of anxiety in some individuals. A survey of dental patients has shown that the fear of pain, the fear of needles, difficulty in achieving anaesthesia and anxiety are major problems for them.[123] Numerous investigations have been performed to increase dentists' abilities to manage pain during root canal treatment.

Pain control during root canal treatment is essential for several reasons. First, patients desire and expect that their treatment should be free of discomfort. Second, good intra-operative pain control helps to reduce post-operative pain[125] and simplifies its management. Third, patients will be reluctant to have further root canal treatment in the future if they have had a bad experience as a result of pain during treatment. Hence, pain-free treatment should be every dentist's aim.

Local anaesthesia is the most common method used for pain control during root canal treatment. However, other strategies can also be employed in some cases – such as pre-treatment anti-inflammatory systemic medications, and methods to reduce discomfort associated with injections.

Pain management during treatment can be approached via three mechanisms – by blocking nociceptive impulses in the peripheral nerves, by reducing nociceptive input from the treatment site and by preventing pain perception in the central nervous system (CNS). Local anaesthetics block nociceptive impulses that are generated during treatment [126] and the nociceptive input can be reduced by using non-steroidal anti-inflammatory drugs (NSAIDs) since they prevent the formation of prostaglandins at the site of treatment or injury.[127] Both of these approaches (especially if a long-acting local anaesthetic agent is used) can prevent pain perception in the CNS post-operatively.[128]

Various strategies can be used to help achieve good pain control during root canal treatment. In most cases, more than one approach will be required. This will be

dependent on the individual patient (anxiety, pre-operative level of pain, pain threshold, etc.), the condition being treated (e.g. acute irreversible pulpitis), the tooth being treated, the anaesthetic solutions available, the time available, etc. Some possible strategies are outlined below.

Acute irreversible pulpitis is generally considered to be the most difficult condition to manage in dentistry with respect to pain control during and after treatment, and especially in mandibular molar teeth. Patients with this condition usually present with a considerable degree of pain – therefore, it is more likely that patients with acute irreversible pulpitis will experience pain during treatment.[128]

Pre-operative strategies

Good pain management begins with having an accurate diagnosis which in turn relies on gathering all the required information to formulate the diagnosis. This includes obtaining a detailed history from the patient regarding the nature of the presenting problem. The history and the patient's description of any symptoms should enable the clinician to make a provisional diagnosis prior to conducting a thorough clinical examination. The clinical examination must include all relevant diagnostic tests plus periapical radiographs. When assessing pulp, root canal and periapical conditions, it is essential to do pulp sensibility testing (preferably with at least two tests such as a cold test and an electric pulp test), probing of the tooth and all restoration margins, percussion, palpation, mobility, periodontal probing, transillumination and biting tests. Periapical radiographs are essential to assess the peri-radicular tissues plus they help to determine the cause of the disease. It is essential to know and understand the conditions being treated. Some conditions may not be associated with pain during treatment or there may only be minimal pain that is easily controlled (e.g. a pulpless, infected root canal system with chronic apical periodontitis), while with other conditions, it may be extremely difficult to manage intraoperative and post-operative pain (e.g. acute irreversible pulpitis with primary acute apical periodontitis). As a general rule, the more pre-operative pain that is reported by the patient, then the more difficult it will be to obtain adequate local anaesthesia and the post-operative pain is likely to be greater.[129]

Premedication

Following diagnosis, consideration should be given to the use of pre-operative medication to reduce pain and inflammation at the treatment site. Several studies have been performed to investigate the effectiveness of this approach using a variety of drugs such as benzodiazepines, NSAIDs and corticosteroids. Premedication with benzodiazepines have been used in an attempt to reduce anxiety prior to treatment.[130] However, generally no significant benefits have been reported on the success of inferior alveolar nerve blocks (IANB) to treat irreversible pulpitis in mandibular molars[131].

The concept of using NSAIDs and corticosteroids as premedication is largely based on reducing the amount of prostaglandin in the inflamed pulp. There have been conflicting results reported for the use of ibuprofen premedication with some studies reporting an increased success rate for local anaesthesia, while others have reported no effects compared with placebo.[132] The different findings may be related to differences in methodology between the studies, but they may also be related to the conditions being treated. In the study by Parirokh et al., only irreversible pulpitis cases that had no spontaneous pain were included and they reported a significant benefit from premedication with ibuprofen. Other studies have used spontaneous pain as an indicator of irreversible pulpitis, and they have typically found no effect from the ibuprofen.[133] Parirokh et al. suggested that spontaneous pain indicated that more advanced inflammation was present in the pulp, and the previously formed tetrodotoxin-resistant (TTX-resistant) sodium channels were not affected by the ibuprofen. However, in earlier stages of irreversible pulpitis when there is no spontaneous pain, these channels have yet to form, and therefore, premedication appears to help increase the success of local anaesthesia. This finding highlights the need to take a thorough history of the patient's presenting condition, so effective pain management strategies can be utilised. The type and dose of premedication may affect the usefulness of this approach. A meta-analysis concluded that 600–800 mg ibuprofen, 75 mg indomethacin, 8 mg lornoxicam, and 50 mg of diclofenac potassium significantly increased the success rate of IANB. However, other NSAIDs such as ketorolac, a combination of ibuprofen and acetaminophen, and acetaminophen alone

had no significant effect compared with placebo.[134] Ibuprofen is generally considered to be a safer drug with few side effects. It is also readily available and therefore is the recommended drug if premedication is to be used. Corticosteroids have only been investigated in two studies: one reported a significant effect on IANB anaesthesia while the other reported no significant difference.[135] However, not all patients had adequate anaesthesia, and the risks associated with using this type of medication need careful consideration.[136]

Topical anaesthesia

Another pre-operative strategy is the use of topical anaesthesia prior to local anaesthetic injections. Many studies have assessed the value of using topical anaesthesia in reducing the pain of injections, but there is no general agreement on whether they decrease the pain of needle insertion and the pain during the injection itself. The results may also be related to other factors such as the site of injection, the time of application of the topical solution, and the agent used. Positive effects of topical anaesthesia have not been demonstrated for palatal injections or for IANB injections.[137] Greater effects have been demonstrated when formulations contain 60% lignocaine or a combination of 2.5% lignocaine and 2.5% prilocaine compared with 20% benzocaine.[138] Topical anaesthetics can also have a placebo effect and demonstrate to the patient that the treating dentist is concerned about the patient's comfort during treatment.

Injection strategies

Notwithstanding the above findings, it is difficult to investigate the individual value of topical anaesthesia or any other factor as each factor is involved in every injection. Pain during injection may be related to the type of anaesthetic, the injection site, the needle size, the injection speed and the use of topical anaesthesia. Different local anaesthetic solutions have different pH values. Lower pH solutions are thought to cause a burning sensation due to their acidic content. Only a few randomised double-blinded studies have investigated the pain on injection of different anaesthetic solutions.[139] They reported that prilocaine, articaine and plain lignocaine had lower pain levels than 2% lignocaine with adrenaline (1:80 000 or 1:100 000). Studies with

high levels of evidence have reported no significant differences in injection pain with different anaesthetic solutions. When the effects of the injection site are considered, maxillary buccal infiltration injections are usually thought to induce significantly less pain than IANB injections but this was not the case in the only randomised double-blinded study that has investigated this. If the injection site has less connective tissue (e.g. palatal in the maxilla), the type of solution had no effect on injection pain. In adults, the size of the needle did not significantly affect the amount of injection pain when three different needles sizes (25, 27 and 30 gauges) were compared during IANB injections and for both buccal and palatal maxillary infiltration injections.[140] In children, smaller needles (30 gauges) produced less discomfort and crying than a 27 gauge needle when used for IANB injections, but there was no difference for infiltrations in the maxilla.[141] The effects of the injection speed on the success of anaesthesia are variable but faster injections do cause more pain.[142]

Intra-operative strategies

Unfortunately, it is not always possible to have completely pain-free root canal treatment as demonstrated by several studies that have investigated the prevalence and degree of pain during root canal treatment.[143] Moderate to severe pain has ranged from 11% to 35% and even as high as 100% in one study.[144] Unfortunately, different criteria have been used in the various studies and this can be misleading – for example, some studies classify 'no or mild pain' as successful anaesthesia,[145] and others report all levels of pain. The amount of pain experienced during treatment is related to the condition being treated – teeth with irreversible pulpitis and acute apical periodontitis were significantly associated with more treatment pain than teeth that had pulpless and infected canals with apical periodontitis. In another study, molars and teeth with irreversible pulpitis had more intra-operative pain than single-rooted teeth and teeth with pulpless, infected root canals. Hence, it is imperative that dentists strive to improve the treatment experience for their patients by utilising strategies to reduce pain during treatment. The essence to this also lies in having an accurate diagnosis and a thorough understanding of the various conditions that affect the pulp and root canal system.

Studies regarding the success of local anaesthetic injections vary in their methodology – some have assessed effectiveness for teeth with healthy pulps, while others have assessed teeth with irreversible pulpitis, which is generally considered to be the most difficult condition to anaesthetise. Some studies have been performed on maxillary teeth while others have been done with mandibular teeth. It is generally considered that mandibular teeth are more difficult to anaesthetise.[146] Hence, the methodology plays an important role when considering the effectiveness of the various injection techniques and or solutions.

Assessing pulp anaesthesia with electric pulp tests or cold tests is a valid, but limited, method. It is valid as there are no other methods available apart from commencing treatment and observing whether the patient feels pain. Pulp testing is limited because the tests are not good indicators of successful anaesthesia as shown in several studies where pain during treatment was felt by the patients despite not responding to pulp tests after time intervals of up to 15 min following injection. This may be a result of different nerve fibres responding to different stimuli. Responses to electric and cold tests are related to fast and slow silent A delta-fibres, respectively, and not the deeper nociceptive C-fibres which are associated with the TTX-resistant sodium channels. The TTX-resistant sodium channels are affected by the prostaglandins released during inflammation, and they decrease the nerve responses to anaesthetics. Hence, the C-fibres may still be active despite the lack of response from the A delta-fibres to electric or cold pulp tests.

Time for anaesthesia

The first step following administration of local anaesthetic is to allow sufficient time for the drug to have its full effect within the tissues. This has practical concerns since patients who present with pain may not have a scheduled appointment, and therefore, the dentist is trying to manage this problem among the regular patients for that day. However, this should not be a reason to rush the treatment, and allowing sufficient time for the local anaesthetic to be effective is paramount to having good pain control during treatment. The time of onset for local anaesthetics in dentistry has not been well researched. According to Malamed, onset varies for each anaesthetic drug with the common ones (lignocaine, prilocaine, articaine, mepivacaine) requiring

approximately 2–4 min.[147] However, studies indicate that longer and varying times are required to achieve adequate pulp anaesthesia – such as 4.2 to 7.4 minutes for articaine with 1:100,000 adrenaline, and 4.7 to 8.0 [148] minutes for articaine with 1:200,000 adrenaline. These studies used electric pulp testing to assess pulp anaesthesia which has some limitations, as discussed above, and the actual times needed for teeth with acute irreversible pulpitis may be much longer. Hence, clinicians should be prepared to wait for periods of up to at least 15 min before commencing treatment, and many cases may require even longer times for onset.

Type of anaesthetic

The type of local anaesthetic solution used may have some bearing on the outcome of the injection. Three studies have investigated local anaesthesia of maxillary anterior, premolar and molar teeth with irreversible pulpitis. In two of these studies, there was no difference between 4% articaine with 1:100,000 adrenaline and 2% lignocaine with either 1:80,000 or 1:100,000[149] adrenaline. However, the other study reported a higher rate of success for articaine for molars and premolars.[150] Unfortunately, there is insufficient evidence available at present to show that any particular local anaesthetic solution is superior to others for maxillary teeth with irreversible pulpitis.

Studies regarding anaesthetic solutions for mandibular teeth with irreversible pulpitis have reported no significant differences when using 4% articaine with 1:100,000 adrenaline and 2% lignocaine with 1:100,000 adrenaline using the Gow-Gates mandibular block and the IANB injection techniques.[151] No significant differences were reported between 0.5% bupivacaine and etidocaine, both with 1:200,000 epinephrine ,[152] as well as between 0.5% bupivacaine with 1:200,000 adrenaline and 2% lignocaine with 1:100,000 adrenaline.[153] Hence, there is also insufficient evidence available at present to show that any particular local anaesthetic solution is superior to others when used for block injections for mandibular teeth with irreversible pulpitis. However, four systematic reviews have reported that articaine is superior to lignocaine when used for buccal infiltration injections for mandibular posterior teeth with irreversible pulpitis.[154]

Additives to local anaesthetics

There has been some interest in the use of additives to local anaesthetic solutions to improve the success rate of injections. However, dexamethasone did not improve anaesthesia for mandibular molars with irreversible pulpitis and the addition of ketorolac to articaine did not provide any added advantages over using articaine alone. Another study reported that there was severe pain during injection when an NSAID was added to the anaesthetic solution.[155] Previous investigations on buffering of anaesthetic solutions used the buffering agent simultaneously with the anaesthetic solutions. However, when the buffering agent was used in combination with 2% lignocaine administrated via infiltration injection 15 min prior to an IANB injection, a significantly higher rate of anaesthetic success was achieved in mandibular first molars with acute irreversible pulpitis.[156] The addition of sodium bicarbonate to buffer the acidic nature of 2% lignocaine did not reduce the pain of injection, and it did not reduce the onset of anaesthesia when used as a maxillary infiltration injection.[157] Trismus and post-operative pain was reported when hyaluronidase was added to lignocaine, and it did not improve the success rate of anaesthesia.[158] There were some positive effects on the success rate of anaesthesia when mannitol was added to some anaesthetic solutions for both normal pulps and those with irreversible pulpitis[159] as a result of its ability to temporarily dissolve the perineural membrane. However, while some positive effects were shown, further research is required to determine whether there are true benefits and also to assess the risks associated with combinations of such drugs.

Volume of local anaesthetic

The volume of local anaesthetic solution injected into the tissues plays a role in achieving adequate anaesthesia. This has been investigated in many studies although there are conflicting results. Two studies[160] have reported that a greater volume of solution significantly improved the rate of success of local anaesthesia when treating teeth with irreversible pulpitis in the mandible using IANB injections, but two other studies reported no difference.[161] The type of anaesthetic solution may be important as three of these four studies used 2% lignocaine with either 1:200,000, 1:100,000 or 1:80,000 adrenaline with conflicting results,[162] and the single study that used 4%

articaine with 1:100,000 adrenaline showed a significantly higher success rate when the volume of the solution was increased. A recent systematic review and meta-analysis was not able to show a significant impact of using different volumes of anaesthetic solutions plus there was no difference between using articaine or lignocaine.[163] However, despite these results, it has been reported that using two cartridges of anaesthetic solution for IANB injections can significantly increase the success of anaesthesia for endodontic treatment in patients with no symptoms as well as those with irreversible pulpitis.[164]

An alternate method of using a higher volume of anaesthetic solution is to use a supplementary injection[165] – that is, another injection administered at a different site, usually with the aim of targeting different nerves, or a different part of the same nerve.

Supplementary injections

The standard local anaesthetic injections used by most dentists do not always provide adequate anaesthesia. This is particularly problematic when treating acute irreversible pulpitis, as demonstrated by Nusstein et al.[165] who reported that only 17 of 25 (68%) patients had no pain following buccal infiltration injections to treat maxillary teeth and only 2 of 26 (7.7%) patients had no pain following an IANB for mandibular teeth. Hence, many patients will require supplementary local anaesthetic injections in order to effectively manage their intraoperative pain.

In the mandible, common supplementary injections are buccal infiltrations and intra-periodontal ligament (intra-PDL) injections. The latter technique is discussed further below. Supplementary buccal infiltrations are used as infiltration injections and also to target the long buccal nerve. There are conflicting results from studies that have investigated the use of buccal infiltrations. Some have found that 4% articaine significantly improved the rate of successful anaesthesia for mandibular molars with irreversible pulpitis compared with the use of 2% lignocaine,[166] while others have found no difference between these two solutions.[167] Overall, several systematic reviews and meta-analyses tend to suggest that articaine is the solution of choice for supplementary buccal infiltrations when treating mandibular posterior teeth with

irreversible pulpitis, but there is no advantage in increasing the volume as one cartridge was just as effective as two.[168]

Other forms of supplementary injections in the mandible include the use of different block techniques such as the Gow-Gates mandibular nerve block which targets the mandibular division of the trigeminal nerve before it splits into its branches (IAN, lingual and long buccal nerves). This injection technique has been reported to have a high rate of success when managing teeth with normal pulps[169] and for third molar surgery although it has slower rate of onset of anaesthesia.[170] In mandibular teeth with irreversible pulpitis, the Gow-Gates technique achieved lip numbness and pulp anaesthesia significantly more often than the Vazirani-Akinosi technique[171] and it was superior to the IANB injection, as well as buccal and lingual infiltrations.[172] However, two other studies have reported no significant differences between the Gow-Gates block and the IANB injection.[173]

When treating mandibular incisors that have inadequate anaesthesia, using a combination of labial and lingual infiltrations as supplementary injections has been reported to provide significantly better anaesthesia than if just one of these infiltrations is used alone.[174]

In the maxilla, a number of supplementary injections can be used when traditional infiltrations have not been fully effective. The palatal anterior superior alveolar (ASAN) block injection can be used for maxillary incisors and canines, but this injection may be painful during needle insertion as well as during and after injection. Swelling, numbness and paraesthesia of the incisive papilla have been reported, so care needs to be taken with this injection technique.[175]

The anterior middle superior alveolar nerve (AMSAN) block injection is another supplementary injection for maxillary anterior teeth and for maxillary premolars. The injection site is located on the palate, about halfway between the midline and the crest of the free gingival margin on a line that bisects the premolars.[176] It has been reported to have moderate to low success rates when used alone,[177] but when combined with a labial or buccal infiltration, it acts as a supplementary injection that can improve the rate of successful anaesthesia.

In maxillary molars, it has been shown that pain associated with treating the pulp in the palatal canal is the common reason for inadequate anaesthesia in teeth with irreversible pulpitis.[178] One way to try and overcome this is to do a pulpectomy for the palatal root as soon as possible upon gaining access to the pulp chamber. Anaesthesia success and duration of action can be improved for maxillary molars by using a supplementary palatal injection following a buccal infiltration.[179] It is likely that the palatal injection acts as an infiltration for the palatal root which lies some distance from the buccal injection site. As the anaesthetic has to diffuse through the bone to reach the root apex, the volume of anaesthetic drug that reaches the target nerves will be reduced as the distance increases. The presence of the maxillary sinus between the buccal and palatal roots may further reduce the amount of solution that diffuses to the palatal root. Hence, by injecting on the palate, the solution is placed closer to the intended target nerve tissue for the palatal root. Another consideration when treating maxillary first molars is to inject twice on the buccal – one infiltration over the apex of the mesio-buccal (MB) root and the second infiltration over the apex of the disto-buccal (DB) root. This approach may overcome the lower diffusion of the anaesthetic solution that can be associated with the thicker bone of the zygomatic process that often lies between these two roots. Although these supplementary injections are often used by clinicians, there are little data available with only one study comparing posterior superior alveolar nerve blocks, buccal infiltrations and buccal plus palatal infiltrations for maxillary first molars with irreversible pulpitis and no significant difference was reported.[180]

Another variable affecting the success of local anaesthesia in maxillary teeth with irreversible pulpitis is the length of the roots of maxillary first molars. In cases with longer roots, particularly for the palatal and DB roots, anaesthesia is less likely to be successful. It was not possible to determine a 'cut-off' length where root length became critical but longer roots were more difficult to anaesthetise than shorter roots.[181] Hence, when radiographs indicate longer roots of maxillary molars, practitioners should consider supplementary anaesthetic techniques in advance, so patients are less likely to experience pain during treatment.

Intra-osseous injections have been used for many years to assist with obtaining adequate local anaesthesia. The intra-PDL injection is a very convenient form of intraosseous injection as the anaesthetic solution passes through the alveolar bone to reach the periapical region and not through the periodontal ligament as is often thought. The intra-PDL injection is the most popular technique used by members of the AAE as a supplementary injection.[182] It is a convenient technique as the site of the injection (i.e. the PDL, via the gingival sulcus) is easily identified and accessed. It is also a simple technique that is easy to learn and administer. The standard dental syringe can be used although some special syringes have been developed for this technique. The technique involves positioning the needle in the PDL at several points around the circumference of the tooth – typically at the MB, DB, mesio-lingual and disto-lingual aspects of the tooth being treated. In mandibular molars, the buccal and lingual furcations (i.e. mid-buccal, midlingual) are extra sites that can be used. The injection must be done with considerable force.[183] If resistance to injection is not felt by the clinician, then the injection does not usually work. This technique works very rapidly – usually within 30 sec[184] – so clinicians should be ready to commence treatment almost as soon as they complete the injection in order to take advantage of it before the anaesthetic effect wears off. Using an intraligamentary injection in conjunction with an IANB has been reported to increase the success rate of anaesthesia.[185] In two studies of posterior mandibular teeth with irreversible pulpitis that had unsuccessful anaesthesia with conventional techniques, the use of supplementary intraligamentary injections resulted in 56–70% having successful anaesthesia.[186] The volume used for an intraligamentary injection plays an important role as 0.6 mL of 2% lignocaine with 1:80,000 adrenaline significantly improved the rate of success of anaesthesia in mandibular molars with irreversible pulpitis during access cavity preparation compared with the use of 0.2 mL of the same solution.[187]

Combining an IANB injection with two supplementary injections – that is, a buccal infiltration injection and then an intra-PDL injection – has been reported to significantly increase the rate of success of local anaesthesia for mandibular molars with irreversible pulpitis. This approach combines the effects of extra (i.e. supplementary) injections, greater volumes of anaesthetic solution and different injection sites that target different nerves or different parts of the nerve.

Another form of intra-osseous injection is when a specific device is used to create an opening in the bone where a needle can be placed to deliver the anaesthetic. When special devices are used to create such an opening, there is a risk of damaging the tooth roots. There are also other possible side effects – including increased heart rate,[188] post-operative infection, plus pain and discomfort after the injection. It is also difficult to use this technique when rubber dam is being used. Examples of special devices for intra-osseous injections are the Stabident (Fairfax Dental Inc., Miami, FL, USA), X-Tip (Dentsply International Inc, Tulsa, OK, USA), IntraFlow (Pro-Dex Inc, Santa Ana, CA, USA) devices. Unfortunately, most studies that have assessed intra-osseous injections were performed on teeth with clinically normal pulps[189] or they combined the results of teeth requiring restorations, root canal treatment and extractions in children and adolescents.[190] One study of teeth with irreversible pulpitis reported no pain after supplementary intra-osseous injections for two of three maxillary posterior teeth where patients had inadequate anaesthesia following infiltration injections and 19 of 21 mandibular posterior teeth for an overall success rate of 88%. However, the number of patients who had intra-osseous injections in this study was quite low, and therefore, the results should be interpreted with caution. Hence, the true effectiveness of the intra-osseous technique using devices to perforate the bone for teeth with irreversible pulpitis is unknown. Despite this, it is still an alternative technique that can be used as a supplementary injection when other techniques have not been successful.

The intra-pulp injection should be considered as a 'last resort injection' to gain sufficient anaesthesia to enable root canal treatment to be commenced. It is considered to be the most painful injection in endodontics and is usually only administered when the patient feels pain during access cavity preparation or when the canals are being instrumented. Clinicians should carefully evaluate the patient's reactions when the access cavity is being prepared. If the patient feels pain on reaching dentine, then there is a high chance that they may feel pain on reaching the pulp. In such cases, it is wise to aim for a very small pulp exposure and to then administer an intra-pulp injection before proceeding further. Having a small exposure – just sufficient for insertion of the needle – allows the injection to be done with pressure. This is a key aspect of this technique as the pressure forces the anaesthetic

solution into the pulp tissue. If no pressure is obtained, then the injection will not work. Two studies have demonstrated the benefits of pressure during injection when they injected saline under pressure and this resulted in pulp anaesthesia.[191] Anaesthesia is immediate and its duration is short[192] – hence, the clinician needs to operate efficiently to remove the pulp.

Intra-pulpal injections should only be used in cases of irreversible pulpitis. They should not be used where there is an infected root canal system – such as when there is partial pulp necrosis or necrobiosis – since the anaesthetic solution has been shown to reach the apical foramen[193] and hence bacteria or debris may be forcefully extruded into the periapical tissues. It has also been suggested that intra-pulp injections are less likely to be successful in teeth with small pulp chambers, particularly in elderly patients.[194]

If adequate pain control is still not achieved with all of the above techniques, then the application of topical anaesthetic gel into the root canal has been suggested in a clinical technique paper – however, no data were presented to indicate its effectiveness.[195] The gel can be placed with a root canal file, but it is likely to be painful during placement and care is required to prevent it being extruded apically. The gel needs to be thoroughly removed via irrigants following canal instrumentation, so it does not affect the subsequent use of medicaments or adhesion of the root canal cement.

Clinicians should be ready to provide supplementary anaesthesia whenever a patient experiences pain during treatment since a single injection often does not provide the level of anaesthesia required. However, unfortunately, none of the supplementary techniques completely overcome pain during treatment as shown by Kayaoglu et al.[196] who reported that 22% of patients had pain after the initial injections and this reduced to 6% after supplementary anaesthesia was provided. Therefore, several forms of supplementary anaesthesia may be required, especially for teeth with irreversible pulpitis. When treating lower molars, these may include a Gow-Gates mandibular nerve block, an IANB injection, a buccal infiltration, a lingual infiltration, an intra-ligamentary injection and an intra-pulp injection. In maxillary molars, it may be

necessary to use two buccal infiltrations (over the MB and DB root apices), a palatal infiltration, an intra-ligamentary injection and an intra-pulp injection.

Managing pain during treatment

Management of a patient requiring root canal treatment where pain may be experienced needs careful consideration and planning. The times when a patient may feel pain are usually: 1. Prior to treatment (e.g. by testing with a cold stimulus) 2. On initial cutting of the tooth or restoration (often due to the cold water of the handpiece) 3. On reaching dentine 4. On reaching the pulp chamber 5. During negotiation and instrumentation of the root canals.

It is important, and good practice, to test a tooth after administering local anaesthetic and waiting for at least 15 min. Since cold stimuli usually cause pain with irreversible pulpitis, it is logical to test the tooth with something cold to determine whether adequate anaesthesia has been achieved. Simply blowing cold air on the tooth with a triplex syringe may be sufficient, but dry ice or a cold spray used for pulp sensibility testing are usually more accurate as the cold sensation is applied directly to just the involved tooth. If the patient does not feel pain with such a test, then treatment can begin although anaesthesia is not guaranteed, as demonstrated by many studies. On the contrary, if the patient still feels pain with the cold test, then this is a good indication to provide supplementary anaesthesia prior to further pulp testing although one study reported that some patients had no pain during root canal treatment despite the pulps responding to electric pulp tests after IANB injections.

In some cases, several forms of supplementary anaesthesia may be required, as outlined above. It is advisable to provide supplementary blocks and infiltrations early in the treatment procedure to not only improve the experience for the patient by having pain-free treatment, but also because once the rubber dam has been placed it is not very convenient to provide further such injections. In addition, it is recommended to place the rubber dam using the cuff technique as this allows easy access to the gingivae in order to give intra-PDL injections as supplementary injections during treatment should they become necessary. The concept of the rubber dam cuff technique is to place the rubber dam clamp on a tooth distal to the one being treated,

and to stretch the rubber dam over several teeth without passing it through every contact point. On the mesial aspect of the cuff, the contact point can usually retain the dam without the need for a second clamp. This technique is easily done by punching several overlapping holes in the dam. Compared with the single tooth isolation technique, the cuff technique provides complete and increased access to the tooth being treated and allows intra-ligamentary injections to be given, if necessary.

Once sufficient anaesthesia is indicated by cold pulp testing, the root canal treatment can be commenced. Since the aim of treatment is to remove the inflamed pulp, there is no need to use the water spray in the high-speed handpiece as there is no need to protect the pulp. By turning off the water spray, the tooth will not be subjected to the coldness of the water and this can make treatment more comfortable for the patient. Many dentists are reluctant to do this, but with a new (i.e. sharp) bur and light cutting strokes/pressure, there should be minimal heat generated so the tooth structure will not be affected.

If the patient feels pain on reaching dentine, intra-ligamentary injections should be given. If they have already been given, then further injections will be required as the duration of action is sometimes short with this technique. The onset of anaesthesia is quite rapid, so treatment can re-commence within 1 min of administration. In most cases, this will allow the clinician to reach the pulp.

If pain is felt on reaching the pulp, then this is an indication for an intra-pulpal injection. As outlined above, the clinician should aim for a small pulp exposure initially in teeth that have been difficult to anaesthetise. The exposure should be just large enough for the needle to be inserted on order to be able to perform the injection with pressure. There is essentially only one opportunity to give an ideal intra-pulp injection under pressure – so a pre-emptive approach is recommended. That is, when dealing with a tooth that is difficult to anaesthetise, clinicians should plan to create a small pulp exposure and then do an intra-pulp injection immediately after exposing the pulp. If not given at that time, then the injection will likely be less successful as it is difficult to create the pressure required. The injection will also likely be more painful since the needle will need to be inserted into each root canal until pressure can be generated.

In multi-canal teeth, each canal will need such an injection, thus increasing the pain even further.

If the intra-pulp injection still does not provide adequate anaesthesia, then topical anaesthetic can be used. However, this is also painful for the patient. A more considerate approach may be to simply perform a pulpotomy to remove the most coronal (and usually the most inflamed) tissue and then place a sedative dressing. In particular, the use of a corticosteroid-antibiotic medicament is advisable since these have been shown to be very effective in reducing post-operative pain.[197] When providing root canal treatment to teeth, it is essential to remove the cause of the presenting complaint. Irreversible pulpitis is usually caused by caries, cracks or breakdown of restorations – all of which allow bacteria and nutrients to enter the tooth and irritate the pulp. Hence, all existing restorations, caries and cracks should be removed as part of the initial treatment. The tooth should then be assessed to determine whether there is adequate tooth structure to enable a new restoration to be placed following the root canal treatment. If the tooth is suitable for further treatment, an interim restoration placed must be placed to prevent bacteria and nutrients from entering the tooth, as well as providing a sound base for further root canal treatment at subsequent appointments.[198] This approach not only removes the causes of the diseases, but it also helps to reduce postoperative pain since there will be no further irritants to any remaining pulp tissue. Likewise, this same approach should be followed when treating teeth that have infected root canal systems and apical periodontitis.

In summary, there are various local anaesthetic injections and other strategies that can be used during root canal treatment to improve the patient experience by reducing the amount of pain felt. However, there are conflicting results among the many studies and every patient will have his/her own perceptions, levels of anxiety and pain-coping methods. In addition, the amount of inflammation within the pulp will vary from tooth to tooth and this will depend on many factors such as when the patient presents for treatment, how long the irritant has been present, etc. Hence, it is difficult to provide definitive guidelines or recommendations that will be successful in all cases. Notwithstanding this, a recent systematic review and meta-analysis[199] regarding pain

control during root canal treatment of lower molars with irreversible pulpitis indicated that increasing the volume of anaesthetic and using premedication with NSAIDs provided the most predictable pulp anaesthesia and pain control. Supplementary injections are also very helpful and usually essential.

Post-operative strategies

Patients who present with moderate to severe pain are five times more likely to experience moderate–severe operative and post-operative pain, even if ideal treatment is provided. In addition, patients who experience pain during treatment (such as when local anaesthesia is inadequate are more likely to have postoperative pain. Hence, clinicians should advise their patients regarding post-operative pain management when treating painful conditions such as irreversible pulpitis. A flexible analgesic strategy is required and this is usually best achieved with NSAIDs such as ibuprofen, provided an adequate dose is taken.[200] Ideally, ibuprofen should be taken as a 400 mg dose every 4 h for adults, assuming there are no contra-indications to this drug.[201] In cases where moderate pain is anticipated, paracetamol can be added (1000 mg every 4 h) to the drug regime. If severe pain is anticipated, then codeine (60 mg every 4 h) can also be taken in addition to the ibuprofen and paracetamol. In this latter situation, the ibuprofen and paracetamol/codeine can be alternated on a 2 hourly basis to achieve and maintain good pain control – for example, have the patient take the ibuprofen immediately after the treatment, then the paracetamol/codeine 2 h later, followed by ibuprofen after another 2 h, paracetamol/codeine after a further 2 h, then ibuprofen again after another 2 h, etc. If adequate treatment has been provided, the systemic use of NSAIDs and analgesics can usually be stopped the following day, or within 2–3 days at the most. If the patient cannot use NSAIDs, then paracetamol and codeine are the drugs of choice for post-operative pain management. A very important aspect of pain management is to commence the pain relief medication immediately on completion of the treatment as this significantly decreases the chance of post-operative pain.[202]

Many patients present for treatment with chronic irreversible pulpitis or other conditions where there are no symptoms or mild, occasional symptoms. In these cases, there is no need to prescribe the regular use of NSAIDs and/or analgesics as

outlined above. Instead, patients should be advised to only use these medications 'on-demand' – that is, only if and when they actually experience pain from which they want relief. There was no significant difference in post-operative pain levels when the 'on-demand' approach was compared with prescribed use of medications.[203]

Finally, the use of long-acting local anaesthetics may improve the post-operative comfort for patients, especially those with severe pre-operative pain. Bupivacaine is an example of a long-acting local anaesthetic that can provide an increased period of post-operative analgesia for up to 8–10 h following block injections. Patients have even reported reduced pain 48 h after periodontal surgery.[204] The long-acting analgesic effect of bupivacaine is a result of decreasing the potential for central sensitisation in addition to the anaesthesia provided by blocking activation of the unmyelinated C-fibres.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Despite more than 100 years of clinical experience with the prototypic NSAID aspirin, controversy persists over the mechanism(s) of action of these drugs. A major hypothesis familiar to many clinicians is that NSAIDs produce analgesic and anti-inflammatory actions by inhibition of cyclo-oxygenase, thereby reducing the synthesis of arachidonic acid metabolites such as prostaglandins and thromboxanes.[205] However, more recent studies suggest that this important class of analgesics has other actions including inhibition of free radical formation, cytokine synthesis or major cellular signalling pathways mediating inflammatory responses.[206] Recognition of these multiple mechanisms has led to the appreciation that the NSAIDs may have other important therapeutic indications such as inhibition of the growth of cancers.[207] This area of research is rapidly expanding and given the recent recognition of adverse effects attributed to the COX-2 inhibitors, it is likely to continue as a major area of scientific inquiry.

Prostaglandins play a key role in the development of inflammation and pain. Therefore, it is predictable that the NSAIDs have clinical efficacy for reducing acute dental pain and inflammation. In support of this point, numerous double-blind placebo-controlled clinical trials have demonstrated that the NSAIDs are effective for

reducing pain due to surgical,[208] periodontal[209] and endodontic procedures. Moreover, systematic reviews of these studies[210] support the clinical recommendation that NSAIDs should be the analgesics of first choice in patients who can tolerate this class of drugs.

Although the NSAIDs are extremely effective for the management of acute dental pain, several adverse effects can occur. The adverse effect profile of the acute administration of ibuprofen includes gastro-intestinal complaints and somnolence.[211] Acute (3-day preoperative) administration of ibuprofen does not appear to produce any detectable increase in post-operative bleeding as measured by the occurrence of a haematoma or ecchymosis following third molar extraction. Evidence exists to suggest that a cumulative consumption of NSAIDs (but not aspirin) over a lifetime increases the risk of end-stage renal disease.[212] In addition, recent studies suggest that the COX-2 inhibitors, and possibly some of the traditional NSAIDs, may produce prothrombic cardiovascular effects.[213]

NSAIDs such as ibuprofen are effective for treating acute pain and inflammation related to endodontic, surgical, restorative or periodontal procedures. Ibuprofen should be considered the drug of first choice for management of acute inflammatory pain in patients who can tolerate this class of drug. Conventional oral formulations are very effective over a dose range of 200-800 mg (not to exceed a total daily dose of 3200 mg). Although the 800 mg dose produces maximum analgesic effects, clinicians should only consider this dose if the benefit for treating severe intense pain outweighs the increased risks of adverse effects. Under most conditions, 400-600 mg of ibuprofen taken every six hours is very effective for treating moderate inflammatory pain. Rapid absorption formulations (for example, ibuprofen in gel caps) may have particular applications in clinical conditions involving emergency pain patients and the combination of 600mg of ibuprofen with 1000 mg of paracetamol taken every six hours increases pain relief compared with ibuprofen taken alone.

Paracetamol and paracetamol-opioid combinations

Paracetamol (also known as acetaminophen in some countries) acts primarily in the central nervous system (CNS) although neither the site nor the mechanisms of action have been clearly established.[214] It has analgesic and anti-pyretic effects, and it is a weak inhibitor of the cyclo-oxygenase sub-groups COX-1 and COX-2. Paracetamol readily crosses into the cerebrospinal fluid. Within the CNS it works by inhibiting prostaglandin synthesis in the hypothalamus, preventing release of spinal prostaglandin and inhibiting nitric oxide synthesis in macrophages. At therapeutic doses it does not inhibit prostaglandin in the peripheral tissues so there is very little, if any, anti-inflammatory action.[215]

Since paracetamol is metabolized in the liver, patients with liver disease need to take care. Paracetamol can cause liver damage, even with normal therapeutic doses, but fortunately this is rare. Other patients who may have increased toxicity are those with a high alcohol intake and those taking enzyme-inducing drugs (e.g., anti-epileptics and rifampicin). Recent research suggests a relationship exists between the toxicity of chronic paracetamol (end-stage renal disease) and the history of lifetime consumption of the drug. Less is known about toxicity and dosage interval or duration of acutely administered doses although it appears more likely to be toxic if the daily dose exceeds 4000 mg in adults. Despite this, it has been suggested that the use of 6000 mg per day for a short period of time may have therapeutic benefit without unduly increasing risks. Paracetamol may cause prolongation of prothrombin time in patients taking anticoagulants and it can occasionally cause urticarial or erythematous skin rashes, fever or blood dyscrasias. An overdose of paracetamol is defined as a single dose of more than 100mg/kg of body weight. Overdose will produce hepatotoxicity, hypoglycaemia and acute renal tubular necrosis. In adults, a dose of 7.5- 15 mg/kg is considered potentially toxic. The smallest fatal dose recorded in adults was 18 mg/kg.[215] Overdose should be considered as a medical emergency and the patient should be admitted to hospital for urgent treatment.

Paracetamol is rapidly absorbed from the stomach so its peak blood levels are reached within 30-60 minutes. It is non-toxic at therapeutic concentrations – usually reaching 5-20 micrograms/ml in plasma, compared to its toxic concentration of 150

micrograms/ml. Elimination half-life is about two hours and protein binding is insignificant. It is metabolized in the liver and the metabolites are excreted via the kidneys. Tolerance and dependence have not been reported, and paracetamol does not cause the same gastric irritation or the other complications associated with aspirin and other NSAIDs.[215]

There are numerous brands and formulations of paracetamol commercially available and most are available 'over the counter'. Typical preparations contain 500mg of paracetamol in tablet or capsule form, but syrups, elixirs and suppositories are also available. The usual recommended adult dose of paracetamol is 500-1000 mg every four to six hours (up to a maximum of 4000 mg per day). Modified dosing schedules apply to some preparations as they may be 'slow-release' formulations. Paracetamol is one of the most common analgesics used in children. The recommended dose for children is 15 mg/kg orally every four hours.[215] The maximum daily dose should be limited to 90 mg/kg up to a total of 4000 mg. It can also be used rectally in children with a dose of 20 mg/kg.

The opioids (narcotics)

The opioids produce analgesia by activation of opioid receptors. Three major families of opioid receptors have been cloned: the mu, kappa and delta opioid receptors.[216] The mu opioid receptor is activated by most clinically used opioids including codeine, hydrocodeine, oxycodone, hydrocodone, tramadol and morphine. The kappa opioid receptor is activated by drugs such as pentazocine and buprenorphine. No currently approved drugs are selective for the delta receptor. Opioid analgesia occurs by activation of opioid receptors expressed on neurons in supraspinal sites, spinal sites and in peripheral tissue. In general, the opioid receptors are thought to inhibit neuronal activity and their analgesic efficacy is attributed in part to the observation that opioid receptors are expressed at most of the major pain processing areas in the central nervous system. Consequently, systemic administration of opioids produces analgesia by inhibiting pain transmission at multiple areas in the neuraxis.

Opioids are well recognized to produce variable responses in patients, with some patients reporting considerably greater analgesia than others, even after

administration of identical doses. The variability in patient response is an important clinical problem and forms the basis for recommendations that analgesics be prescribed based on patient report rather than on prior expectations of the clinician. The basis for this variability in analgesia is unclear but it is thought to involve both environmental (e.g., psychosocial status, secondary gain, etc), pathophysiological (e.g., liver function, enzyme/receptor expression) and genetic factors. Considerable interest has been raised by pharmacogenetic analysis of opioid analgesia. For example, patients with certain polymorphisms to the cytochrome P450 enzyme (i.e., CYP 2D6) are completely resistant to codeine analgesia (since they cannot convert codeine to morphine), and they are partially resistant to tramadol analgesia.[217] In addition, several polymorphisms to the opioid receptors have been discovered and are associated with altered responses to opioid analgesics or altered reports of pain intensity.[217] Gender is another interesting genetic factor associated with altered opioid responsiveness. Several studies have reported that women demonstrate significantly greater analgesia to kappa opioids (e.g., pentazocine) than men.[218] In addition, a meta-analysis of third molar extraction studies concluded that women report significantly greater pain levels compared with men. Given these factors, clinicians should prescribe drugs based on the patient's reported pain levels. Although a patient's report of pain is not an exact value, it is a useful alternative to prescribing fixed doses to all patients as this invariably leads to some being over-medicated and others experiencing unnecessary pain due to being under-medicated.

The adverse effect profile of the opioids is well recognized and includes nausea, emesis and respiratory depression. Concern has also been raised about opioid abuse and its impact in the dental setting.[219]

Opioids are highly effective analgesics but they also have a concomitant high incidence of side effects. In the clinical setting of treating ambulatory acute dental pain, opioids are used in low dosages that provide relatively minor adverse effects at the cost of reduced analgesia. Given their relative ratio of therapeutic benefits versus risks, the opioids should not be considered as the analgesic of first choice in this setting. Instead, opioids should be used as adjuncts to nonnarcotics that are given at maximally effective dosages (i.e., 1000mg paracetamol). A meta-analysis of the analgesic

literature supports this last point. In one meta-analysis there was a 42 per cent analgesic response in 1123 patients given 600-650mg of paracetamol with 60mg of codeine (response defined as 50 per cent reduction in pain), whereas increasing the non-narcotic dosage to 1000mg of paracetamol combined with 60mg of codeine increased the analgesic response to 57 per cent in 197 patients.

Given the above data, the general recommendation is to consider opioids as adjunctive drugs. Patients who can tolerate NSAIDs such as ibuprofen should be first given maximally effective doses based on the patient's pain report. Patients who cannot tolerate NSAIDs should be given paracetamol combinations with codeine as discussed above.

Corticosteroids

Systemic corticosteroids are rarely indicated in dentistry but they can at times be useful for the management of inflammation. Their use should be reserved for situations where the correct diagnosis has been made, the dental treatment has been provided adequately, no other anti-inflammatory medication has helped and the medical history does not reveal any contraindication to their use. They should also only be used when there are no signs of infection and no possibility of an infection developing. Such situations include emergencies (adrenal crisis, anaphylaxis and allergic reactions), severe post-operative swelling, following severe trauma, periapical nerve sprouting and acute apical periodontitis following removal of an acutely inflamed pulp, severe muscle inflammation associated with temporomandibular dysfunction, and for some oral ulcerations and mucosal lesions that cannot be managed with topical medications.[220]

Corticosteroids can be either glucocorticosteroids or mineralocorticosteroids. Only glucocorticosteroids inhibit immune and inflammatory responses, therefore the latter group will not be discussed in this review. Cortisol is the primary glucocorticoid and it is produced and secreted by the adrenal cortex. Its release is regulated by a complex pathway known as the hypothalamic-hypohyseal portal system which produces adrenocorticotrophic hormone (ACTH). Several synthetic glucocorticoids have been produced and their relative activity and potency vary. Prednisone and prednisolone

are four times more potent as anti-inflammatory agents than cortisol, whilst triamcinolone is five times more potent and dexamethasone is 25 times more potent. The adrenal cortex produces approximately 10mg/day of cortisol in non-stressed adults and under severe stress this may increase more than 10-fold.[221]

Glucocorticoids act to reduce inflammation by inhibiting the production of multiple cells and factors involved in the inflammatory response. They decrease vasoactive and chemotactic factors, decrease secretion of lipolytic and proteolytic enzymes, decrease extravasation of leukocytes to areas of tissue injury and decrease fibrosis. Glucocorticoids also act against the immune response by inhibiting cytokine production. The multiple sites of action of the glucocorticoids has been proposed as the reason for their greater anti-inflammatory and, possibly, greater analgesic effects than the NSAIDs which typically are more selective and only act on one site.[221]

Glucocorticoids have been shown to be very effective in reducing the periapical inflammatory response following endodontic treatment,[222] and studies have shown anti-inflammatory effects in untreated irreversible pulpitis.[223] They have also been shown to reduce bradykinin levels and post-operative pain[224] and oedema in the oral surgery third molar extraction model used in many pain studies.

The glucocorticoids circulate in the blood with 90 per cent or more being reversibly bound to plasma protein. The half-life of cortisol is about 90 minutes and the synthetic forms vary (e.g., prednisone – 60 minutes, prednisolone – 200 minutes, triamcinolone – 300 minutes, dexamethasone – 300 minutes). Metabolism takes place in the liver and they are excreted in the urine.[221]

When glucocorticosteroids are taken systemically, they can potentially affect many organ systems and tissues. However, such effects are usually only associated with supraphysiological doses taken over a long period of time (usually more than two weeks). Schimmer and Parker have stated that 'a single dose of glucocorticoid, even a large one, is virtually without harmful effects and a short course of therapy (up to one week) in the absence of any specific contraindications is unlikely to be harmful'.[221]

Clinicians must be aware that corticosteroids not only reduce inflammation but they also suppress the immune response. This may have adverse effects on the patient's

health and well-being. Wherever possible, the topical use of corticosteroids is preferred since the immunosuppressive effects are much less severe. The glucocorticosteroids should be avoided in patients with systemic fungal infection and known hypersensitivity to the drug being prescribed. They should be used with caution in patients with ulcerative colitis, pyogenic infections, diverticulitis, peptic ulcers, diabetes mellitus, ocular herpes, acute psychosis and tuberculosis. They can cause mild psychological disturbances such as euphoria, insomnia and nervousness but can also cause severe problems such as manic depression and schizophrenic psychosis. These problems are usually related to the size of the dose and the duration.[221] It is important for the dentist to monitor the patient's progress whilst taking corticosteroids since many oral and dental inflammatory conditions are the result of, or are associated with, an infection of some kind (i.e., bacterial, fungal or viral) which may rapidly exacerbate once the inflammatory and immune responses have been suppressed by the corticosteroid. Conditions not resolving within a few days may also warrant referral for specialist assessment and management.

A simple and relatively safe corticosteroid that can be used for oral and dental inflammatory conditions is dexamethasone. It should only be used as an adjunct to dental treatment and not as the sole means of managing the pain. Dexamethasone is available as 4 mg tablets. The usual oral dosing regime is an 8mg loading dose, followed by 4mg every eight hours for two to three days up to a maximum of five days. If the problem has not improved within this time period, then the dentist should review, and possibly revise, the diagnosis and consider other treatment strategies and whether some other condition may be the cause of the inflammation.

CONCLUSION

Good pain control before, during and after root canal treatment is essential for effective patient management. Pain control relies on a combination of strategies which begin with having a thorough understanding of the conditions being treated, making an accurate diagnosis, and the use of premedication with NSAIDs in some cases. Standard local anaesthetic solutions and injection techniques along with increased volumes and specific supplementary injections for the various tooth types will usually enable clinicians to commence root canal treatment and medicate the root canal system to relieve the presenting pain problem. These should then be followed by the use of flexible post-operative pain management strategies that cater for the individual patient and the specific condition(s) being treated.

The ability to effectively manage pain represents a critical skill of the prudent practitioner. Pain management strategies include the '3-D' approach (diagnosis, dental treatment and drugs) that provides a systematic way of evaluating and managing the acute dental pain patient using combined nonpharmacologic and pharmacologic strategies. From this perspective, patients should be treated with NSAIDs or paracetamol (for those patients who cannot tolerate NSAIDs) as the 'first choice' drugs at doses that are proven to be effective in the literature and with a perspective of balancing the patient's analgesic requirements with the potential for adverse effects. Opioids should be considered adjunctive drugs that act to enhance overall analgesia at the cost of increased adverse effects. Corticosteroids can be used in specific situations where the pain is inflammatory in origin, where there is no infection and where there are no contraindications to the chosen drug being used.

REFERENCES

1. Rotpenpian N, Yakkaphan P. Review of literatures: Physiology of Orofacial Pain in dentistry. Eneuro. 2021 Mar;8(2).
2. Bender IB. Pulpal pain diagnosis—a review. Journal of endodontics. 2000 Mar 1;26(3):175-9.
3. Schuh CM, Benso B, Aguayo S. Potential novel strategies for the treatment of dental pulp-derived pain: pharmacological approaches and beyond. Frontiers in Pharmacology. 2019 Sep 18; 10:1068.
4. Kumar KH, Elavarasi P. Definition of pain and classification of pain disorders. J Adv Clin Res Insights 2016; 3:87-90.
5. Hargreaves KM, Cohen S, Berman LH (2011) Cohen's pathways of the pulp. Mosby Elsevier, St. Louis.
6. Brown AC, Beeler WJ, Kloka AC et al (1985) Spatial summation of pre-pain and pain in human teeth. Pain 21(1):1–16.
7. Besson JM, Chaouch A (1987) Peripheral and spinal mechanisms of nociception. Physiol Rev 67(1):67–186
8. Dubner R, Hayes RL, Hoffman DS (1980) Neural and behavioral correlates of pain in the trigeminal system. Res Publ Assoc Res Nerv Ment Dis 58:63-72.
9. Hargreaves KM, Cohen S, Berman LH (2012) Cohen's pathways of the pulp. Mosby Elsevier, St. Louis.
10. Brown AC, Beeler WJ, Kloka AC et al (1985) Spatial summation of pre-pain and pain in human teeth. Pain 21(1):1–16.
11. Durso BC, Israel MS, Janini ME et al (2003) Orofacial pain of cardiac origin: a case report. Cranio 21(2):152–153.
12. Graff-Radford SB (1991) Headache problems that can present as toothache. Dent Clin North Am 35(1):155–170.

13. Hargreaves KM, Goodis HE (2012) Seltzer and Bender's dental pulp. Quintessence, Chicago.

14. Noguchi K, Kawai Y, Fukuoka T, et al. Substance P induced by peripheral nerve injury in primary afferent sensory neurons and its effect on dorsal column nucleus neurons. J Neurosci 1995; 15:7633–43.

15. Olesen J. The international classification of headache disorders. Cephalalgia 2004; 24(Suppl 1):133.

16. Torebjork HI, Lundberg LE, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. J Physiol 1992;448: 765–80.

17. McMahon SB, Koltzenburg M. Silent afferents and visceral pain. In: Fields HL, Liebeskind JC, editors. Pharmacological approaches to the treatment of chronic pain: new concepts and critical issues. Seattle (WA): IASP Press; 1994. p. 11–30.

18. Olszewski J. On the anatomical and functional organization of the trigeminal nucleus. J Comp Neurol 1950; 92:401–13.

19. Beecher HK. Relationship of significance of wound to pain experienced. JAMA 1956;161: 1609–13.

20. Jacobsen PB, Butler RW. Relation of cognitive coping and catastrophizing to acute pain and analgesic use following breast cancer surgery. J Behav Med 1996; 19:17–29.

21. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150:971–9.

22. Torebjork HI, Lundberg LE, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. J Physiol 1992;448: 765–80.

23. Thompson S, Woolf CJ, Sivilotti L. Small caliber afferents produce a heterosynaptic facilitation of the synaptic responses evoked by primary

afferent A fibres in the neonatal rat spinal cord in vitro. J Neurophysiol 1993; 69:2116–28.

24. Woolf CJ. Molecular signals responsible for the reorganization of the synaptic circuitry of the dorsal horn after peripheral nerve injury: the mechanisms of tactile allodynia. In: Barsook D, editor. Molecular neurobiology of pain. Seattle (WA): IASP Press; 1997. p. 171–200.

25. Chong MS, Woolf Clifford J, Haque NS, et al. Axonal regeneration from injured dorsal roots into the spinal cord of adult rats. J Comp Neurol 1999; 410:42–54.

26. Sugimoto T, Bennett GJ, Kajander K. Transsynaptic degeneration in the superficial dorsal horn after sciatic nerve injury: effects of a chronic constriction injury, transection, and strychnine. Pain 1990; 42:201–13.

27. Mao J, Price D, Hayes R, Lu J, et al. Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviors in rad model of peripheral monoeneuropathy. Brain Res 1993; 605:164–8.

28. Hong CZ, Simons DG. Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. Arch Phys Med Rehabil 1998; 79:863–72.

29. Burstein R. Deconstructing migraine headache into peripheral and central sensitization. Pain 2001; 89:107–10.

30. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14: 135–43.

31. Graff-Radford SB, Solberg WK. Atypical odontalgia. CDA J 1986; 14:27–32.

32. Marbach JJ. Is phantom tooth pain a deafferentation (neuropathic) syndrome? Part 1: evidence derived from pathophysiology and treatment. Oral Surg Oral Med Oral Pathol 1993;75(1):95–105.

33. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis 1998; 5:209–27.

34. Henry MA, Hargreaves KM. Peripheral mechanisms of odontogenic pain. Dental Clinics. 2007 Jan 1;51(1):19-44.

35. Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 1993; 124:115–21.

36. Anderson DJ, Hannam AG, Mathews B. Sensory mechanisms in mammalian teeth and their supporting structures. Physiol Rev 1970; 50:171–95.

37. Pashley D, Liewehr F. Structure and functions of the dentin-pulp complex. In: Cohen S, Hargreaves K, editors. Pathways of the pulp. St. Louis (MO): Mosby Elsevier; 2006. p. 460–513.

38. Byers MR, Narhi MV. Dental injury models: experimental tools for understanding neuroinflammatory interactions and polymodal nociceptor functions. Crit Rev Oral Biol Med 1999; 10:4–39.

39. Fearnhead RW. Histological evidence for the innervation of human dentine. J Anat 1957; 91:267–77.

40. Nair PN. Neural elements in dental pulp and dentin. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 80:710–9.

41. Johnsen D, Johns S. Quantitation of nerve fibres in the primary and permanent canine and incisor teeth in man. Arch Oral Biol 1978; 23:825–9.

42. Aars H, Brodin P, Andersen E. A study of cholinergic and beta-adrenergic components in the regulation of blood flow in the tooth pulp and gingiva in man. Acta Physiol Scand 1993; 148:441–7.

43. Sasano T, Shoji N, Kuriwada S, et al. Absence of parasympathetic vasodilatation in cat dental pulp. J Dent Res 1995; 74:1665–70.

44. Olgart L, Gazelius B, Brodin E, et al. Release of substance P-like immunoreactivity from the dental pulp. Acta Physiol Scand 1977; 101:510–2.

45. Rodd HD, Boissonade FM. Immunocytochemical investigation of neurovascular relationships in human tooth pulp. J Anat 2003; 202:195–203.

46. Schoneberg T, Schultz G, Gudermann T. Structural basis of G protein-coupled receptor function. Mol Cell Endocrinol 1999; 151:181–93.

47. Dionne RA, Lepinski AM, Gordon SM, et al. Analgesic effects of peripherally administered opioids in clinical models of acute and chronic inflammation. Clin Pharmacol Ther 2001;70: 66–73.

48. Cerka-Withers K, Patwardhan A, Hargreaves K. Characterization of prostaglandin receptors mediating sensitization of trigeminal nociceptors. J Dent Res 2006;117.

49. Isett J, Reader A, Gallatin E, et al. Effect of an intraosseous injection of depo-medrol on pulpal concentrations of PGE2 and IL-8 in untreated irreversible pulpitis. J Endod 2003; 29:268–71.

50. Takayama S, Miki Y, Shimauchi H, et al. Relationship between prostaglandin E2 concentrations in periapical exudates from root canals and clinical findings of periapical periodontitis. J Endod 1996; 22:677–80.

51. Prescott ED, Julius D. A modular PIP2 binding site as a determinant of capsaicin receptor sensitivity. Science 2003; 300:1284–8.

52. Goodis HE, Bowles WR, Hargreaves KM. Prostaglandin E2 enhances bradykinin-evoked iCGRP release in bovine dental pulp. J Dent Res 2000; 79:1604–7.

53. Yu FH, Yarov-Yarovoy V, Gutman GA, et al. Overview of molecular relationships in the voltage-gated ion channel superfamily. Pharmacol Rev 2005; 57:387–95.

54. Wood JN. Recent advances in understanding molecular mechanisms of primary afferent activation. Gut 2004; 53:9ii–12.

55. Hille B. Ionic channels of excitable membranes. 3rd ed. Sunderland (MA): Sinauer; 2001.

56. McQuay HJ. Neuropathic pain: evidence matters. Eur J Pain 2002;6(Suppl A):11–8.

57. Bielefeldt K, Ozaki N, Whiteis C, et al. Amitriptyline inhibits voltage-sensitive sodium currents in rat gastric sensory neurons. Dig Dis Sci 2002; 47:959–66.

58. Goldin AL, Barchi RL, Caldwell JH, et al. Nomenclature of voltage-gated sodium channels. Neuron 2000; 28:365–8.

59. Goldin AL, Barchi RL, Caldwell JH, et al. Nomenclature of voltage-gated sodium channels. Neuron 2000; 28:365–8

60. Amir R, Argoff CE, Bennett GJ, et al. The role of sodium channels in chronic inflammatory and neuropathic pain. J Pain 2006;7(Suppl 3):S1–29.

61. Waxman SG, Kocsis JD, Black JA. Type III sodium channel mRNA is expressed in embryonic but not adult spinal sensory neurons and is reexpressed following axotomy. J Neurophysiol 1994; 72:466–70.

62. Krzemien DM, Schaller KL, Levinson SR, et al. Immunolocalization of sodium channel isoform NaCh6 in the nervous system. J Comp Neurol 2000; 420:70–83.

63. Akopian A, Sivilotti L, Wood J. A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. Nature 1996; 379:257–62.

64. Gutman GA, Chandy KG, Grissmer S, et al. International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. Pharmacol Rev 2005; 57:473–508.

65. Ocana M, Cendan CM, Cobos EJ, et al. Potassium channels and pain: present realities and future opportunities. Eur J Pharmacol 2004; 500:203–19.

66. Rasband MN, Park EW, Vanderah TW, et al. Distinct potassium channels on pain-sensing neurons. Proc Natl Acad Sci USA 2001; 98:13373–8.

67. Hu HJ, Carrasquillo Y, Karim F, et al. The kv4.2 potassium channel subunit is required for pain plasticity. Neuron 2006; 50:89–100.

68. Catterall WA, Perez-Reyes E, Snutch TP, et al. International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev 2005; 57:411–25.

69. Ertel EA, Campbell KP, Harpold MM, et al. Nomenclature of voltage-gated calcium channels. Neuron 2000; 25:53.

70. Montell C. The TRP superfamily of cation channels. Sci STKE 2005;2005:re3.

71. Clapham DE. Calcium signaling. Cell 1995; 80:259–68.

72. Clapham DE, Julius D, Montell C, et al. International Union of Pharmacology. XLIX. Nomenclature and structure-function relationships of transient receptor potential channels. Pharmacol Rev 2005; 57:427–50.

73. Caterina MJ, Schumacher MA, TominagaM, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997; 389:816–24.

74. Dubner R, Sessle BJ, Storey AT. The Neural Basis of Oral and Facial Function. New York: Plenum, 1978.

75. Plato. Timaeus. Salt Lake City, UT: Project Gutenberg, 1998.

76. Dallenbach KM. Pain: history and present status. Am J Psychol 52: 331–347,1939.

77. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 150: 971–979,1965.

78. Nathan PW, Rudge P. Testing the gate-control theory of pain in man. JNeurol Neurosurg Psychiatry 37: 1366 –1372, 1974.

79. Treede RD. Pain and hyperalgesia: definitions and theories. In: Handbook of Clinical Neurology, edited by Cervero F and Jensen TS. Amsterdam:Elsevier, 2006, vol. 81, p. 3–10.

80. McGrath PA, Gracely RH, Dubner R, Heft MW. Nonpain and pain sensations evoked by tooth pulp stimulation. Pain 1983; 15:377–88.

81. Andrew D, Matthews B. Properties of single nerve fibres that evoke blood flow changes in cat dental pulp. J Physiol 2002; 542:921–8.

82. Trulsson M. Sensory-motor function of human periodontal mechanoreceptors. J Oral Rehabil. 2006; 33:262–73.

83. Nair PN. Neural elements in dental pulp and dentin. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995; 80:710–9.

84. Narhi MV, Hirvonen TJ, Hakumaki MO. Responses of intradental nerve fibres to stimulation of dentine and pulp. Acta Physiol Scand. 1982; 115:173–8.

85. Jyvasjarvi E, Kniffki KD. Cold stimulation of teeth: a comparison between the responses of cat intradental A delta and C fibres and human sensation. J Physiol. 1987; 391:193–207.

86. Sole-Magdalena A, Martinez-Alonso M, Coronado CA, Junquera LM, Cobo J, Vega JA. Molecular basis of dental sensitivity: The odontoblasts are multisensory cells and express multifunctional ion channels. Ann Anat. 2018; 215:20–9.

87. Vongsavan N, Matthews B. The relationship between the discharge of intradental nerves and the rate of fluid flow through dentine in the cat. Arch Oral Biol. 2007; 52:640–7.

88. Park C-K, Kim MS, Fang Z, Li HY, Jung SJ, Choi S-Y et al. Functional expression of thermo-transient receptor potential channels in dental

primary afferent neurons: implication for tooth pain. J Biol chem 2006; 281:17304–11.

89. Hossain MZ, Bakri MM, Yahya F, Ando H, Unno S, Kitagawa J. The role of transient receptor potential (TRP) channels in the transduction of dental pain. Int J Mol Sci 2019; 20:526.

90. Narhi MV. The characteristics of intradental sensory units and their responses to stimulation. J Dent Res 1985; 64:564–571.

91. Caviedes-Bucheli J, Camargo-Beltran C, Gomez-laRotta AM, Moreno SC, Abello GC, Gonzalez-Escobar JM. Expression of calcitonin gene-related peptide (CGRP) in irreversible acute pulpitis. J Endod2004; 30:201–4.

92. Killough SA, Lundy FT, Irwin CR. Substance P expression by human dental pulp fibroblasts: a potential role in neurogenic inflammation. J Endod 2009; 35:73–7.

93. Zhang X, Li L, McNaughton PA. Proinflammatory mediators modulate the heat-activated ion channel TRPV1 via the scaffolding protein AKAP79/150. Neuron 2008; 59:450–61.

94. Luo S, Perry GM, Levinson SR, Henry MA. Nav1.7 expression is increased in painful human dental pulp. Mol Pain 2008; 4:16.

95. Kimberly CL, Byers MR. Inflammation of rat molar pulp and periodontium causes increased calcitonin gene-related peptide and axonal sprouting. Anat Rec 1988; 222:289–300.

96. Zhang S, Chiang CY, Xie YF, Park SJ, Lu Y, Hu JW et al. Central sensitization in thalamic nociceptive neurons induced by mustard oil application to rat molar tooth pulp. Neuroscience 2006; 142:833–42.

97. Sharav Y, Leviner E, Tzukert A, McGrath PA. The spatial distribution, intensity and unpleasantness of acute dental pain. Pain 1984; 20:363–70.

98. Fried K, Sessle BJ, Devor M. The paradox of pain from tooth pulp: low threshold "algoneurons"? Pain 2011; 152:2685–9.

99. Ricucci D, Loghin S, Siqueira JF Jr. Correlation between clinical and histologic pulp diagnoses. J Endod 2014; 40:1932–9.

100. American Association of Endodontists. Endodontic diagnosis. Chicago; 2013.

101. Mejare IA, Axelsson S, Davidson T, Frisk F, Hakeberg M, Kvist T et al. Diagnosis of the condition of the dental pulp: a systematic review. Int Endod J 2012; 45:597–613.

102. Wolters WJ, Duncan HF, Tomson PL, Karim IE, McKenna G, Dorri M et al. Minimally invasive endodontics: a new diagnostic system for assessing pulpitis and subsequent treatment needs. Int Endod J 2017; 50:825–9.

103. Taha NA, Khazali MA. Partial pulpotomy in mature permanent teeth with clinical signs indicative of irreversible pulpitis: a randomized clinical trial. J Endod 2017; 43:1417–21.

104. Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, Smith AJ et al. Dental pulp defence and repair mechanisms in dental caries. Mediators Inflamm 2015; 2015:230251.

105. Kokkas AB, Goulas A, Varsamidis K, Mirtsou V, Tziafas D. Irreversible but not reversible pulpitis is associated with up-regulation of tumour necrosis factoralpha gene expression in human pulp. Int Endod J 2007; 40:198–203.

106. International classification of orofacial pain. 1st edition (ICOP). Cephalalgia 2020; 40:129–221. https://doi. org/10.1177/0333102419893823.

107. Cunha-Cruz J, Wataha JC, Heaton LJ, Rothen M, Sobieraj M, Scott J et al. The prevalence of dentin hypersensitivity in general dental practices in the northwest United States. J Am Dent Assoc 2013; 144:288–96.

108. Absi EG, Addy M, Adams D. Dentine hypersensitivity. A study of the patency of dentinal tubules in sensitive and non-sensitive cervical dentine. J Clin Periodontol 1987; 14:280–4.

109. Brannstrom M, Astrom A. The hydrodynamics of the dentine; its possible relationship to dentinal pain. Int Dent J 1972; 22:219–27.

110. Narhi M, Yamamoto H, Ngassapa D, Hirvonen T. The neurophysiological basis and the role of inflammatory reactions in dentine hypersensitivity. Arch Oral Biol 1994; 39:23s–30s.

111. Kovacevic M, Tamarut T, Jonjic N, Braut A, Kovacevic M. The transition from pulpitis to periapical periodontitis in dogs' teeth. Aust Endod J 2008; 34:12–8.

112. Long H, Liao L, Gao M, Ma W, Zhou Y, Jian F et al. Periodontal CGRP contributes to orofacial pain following experimental tooth movement in rats. Neuropeptides. 2015; 52:31–7.

113. Armada-Dias L, Breda J, Provenzano JC, Breitenbach M, Roc^as IdN, Gahyva SMM et al. Development of periradicular lesions in normal and diabetic rats. Journal of Applied Oral Science 2006; 14:371–5.

114. Kanagasingam S, Lim CX, Yong CP, Mannocci F, Patel S. Diagnostic accuracy of periapical radiography and cone beam computed tomography in detecting apical periodontitis using histopathological findings as a reference standard. Int Endod J 2017; 50:417–26.

115. Herrera D, Roldan S, Gonzalez I, Sanz M. The periodontal abscess (I). Clinical and microbiological findings. J Clin Periodontol 2000; 27:387–94.

116. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH et al. Periodontitis: consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. J Clin Periodontol 2018;45: S162–S70.

117. Liu H, Jiang H, Wang Y. The biological effects of occlusal trauma on the stomatognathic system – a focus on animal studies. J Oral Rehabil 2013; 40:130– 8.

118. Yang SE, Jo AR, Lee HJ, Kim SY. Analysis of the characteristics of cracked teeth and evaluation of pulp status according to periodontal probing depth. BMC Oral Health 2017; 17:135.

119. Cameron CE. Cracked-tooth syndrome. J Am Dent Assoc 1964; 68:405–11.

120. Brannstrom M. The hydrodynamic theory of dentinal pain: sensation in preparations, caries, and the dentinal crack syndrome. J Endod 1986; 12:453–7.

121. Ricucci D, Siqueira JF Jr, Loghin S, Berman LH. The cracked tooth: histopathologic and histobacteriologic aspects. J Endod 2015; 41:343–52.

122. Kakoei S, Parirokh M, Nakhaee N, Jamshidshirazi F, Rad M, Kakooei S. Prevalence of toothache and associated factors: a population-based study in southeast Iran. Iran Endod J 2013; 8: 123–8.

123. Huh YK, Montagnese TA, Harding J, Aminoshariae A, Mickel A. Assessment of patients' awareness and factors influencing patients' demands for sedation in endodontics. J Endod 2015; 41: 182–9.

124. Hargreaves KM, Khan A. Surgical preparation: anesthesia and hemostasis. Endod Topics 2005; 11: 32–55.

125. Meechan JG. Supplementary routes to local anaesthesia. Int Endod J 2002; 35: 885–96.

126. O'Keefe EM. Pain in endodontic therapy: preliminary study. J Endod 1976; 2 315–9.

127. Parirokh M, Yosefi MH, Nakhaee N, Manochehrifar H, Abbott PV, Reza Forghani F. Effect of bupivacaine on postoperative pain for inferior alveolar nerve block anesthesia after single-visit root canal treatment in teeth with irreversible pulpitis. J Endod 2012; 38: 1035–9.

128. Parirokh M, Ashouri R, Rekabi AR et al. The effect of premedication with ibuprofen and indomethacin on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. J Endod 2010; 36: 1450–4.

129. Carter AE, Carter G, George R. Pathways of fear and anxiety in endodontic patients. Int Endod J 2015; 48: 528– 32.

130. Abbott PV, Yu C. A clinical classification of the status of the pulp and the root canal system. Aust Dent J 2007; 52 (Suppl 1): S17–31.

131. Khademi AA, Saatchi M, Minaiyan M, Rostamizadeh N, Sharafi F. Effect of preoperative alprazolam on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. J Endod 2012; 38: 1337–9.

132. Jena A, Shashirekha G. Effect of preoperative medications on the efficacy of inferior alveolar nerve block in patients with irreversible pulpitis: a placebo-controlled clinical study. J Conserv Dent 2013; 16: 171–4.

133. Hargreaves KM, Keiser K. Local anesthetic failure in endodontics. Endod Topics 2002; 1: 26–39.

134. Aggarwal V, Singla M, Kabi D. Comparative evaluation of effect of preoperative oral medication of ibuprofen and ketorolac on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis: a prospective, double-blind, randomized clinical trial. J Endod 2010; 36: 375–8.

135. Li C, Yang X, Ma X, Li L, Shi Z. Preoperative oral nonsteroidal anti-inflammatory drugs for the success of the inferior alveolar nerve block in irreversible pulpitis treatment: a systematic review and meta-analysis based on randomized controlled trials. Quintessence Int 2012; 43: 209–19

136. Reader AN, Hargreaves KM. Local anesthesia in endodontics. In: Hargreaves KM, Cohen S, eds. Pathways of the pulp. 10th edn. St Louis, MO: Mosby Elsevier; 2011. pp. 691–719.

137. Nakanishi O, Haas D, Ishikawa T, Kameyama S, Nishi M. Efficacy of mandibular topical anesthesia varies with the site of administration. Anesth Prog 1996; 43: 14–9

138. Al-Melh MA, Andersson L. Comparison of topical anesthetics (EMLA/Oraqix vs benzocaine) on pain experienced during palatal needle injection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 103: e16–20.

139. Kanaa MD, Whitworth JM, Meechan JG. A comparison of the efficacy of 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:80,000 epinephrine in achieving pulpal anesthesia in maxillary teeth with irreversible pulpitis. J Endod 2012; 38: 279–82.

140. Flanagan T, Wahl MJ, Schmitt MM, Wahl JA. Size doesn't matter: needle gauge and injection pain. Gen Dent 2007; 55: 216–7.

141. Ram D, Hermida BL, Amir E. Reaction of children to dental injection with 27- or 30-gauge needles. Int J Paediatr Dent 2007; 17: 383–7.

142. Kanaa MD, Meechan JG, Corbett IP, Whitworth JM. Speed of injection influences efficacy of inferior alveolar nerve blocks: a double-blind randomized controlled trial in volunteers. J Endod 2006; 32: 919–23.

143. Martin-Gonzalez J, Echevarria-Perez M, Sanchez-Dominguez B et al. Influence of root canal instrumentation and obturation techniques on intra-operative pain during endodontic therapy. Med Oral Patol Oral Cir Bucal 2012; 17: e912–8.

144. Rousseau WH, Clark SJ, Newcomb BE, Walker ED, Eleazer PD, Scheetz JP. A comparison of pain levels during pulpectomy, extractions, and restorative procedures. J Endod 2002; 28: 108–10.

145. Parirokh M, Satvati SA, Sharifi R et al. Efficacy of combining a buccal infiltration with an inferior alveolar nerve block for mandibular molars with irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 109: 468–73.

146. Nusstein JM, Reader A, Drum M. Local anesthesia strategies for the patient with a "hot" tooth. Dent Clin North Am 2010; 54: 237–47.

147. Byers MRHM, Narhi MVO. Dental innervations and its responses to tooth injury. In: Hargreaves KM, Goodis HE, Tay FR, eds. Seltzer and Bender's

dental pulp. 2nd ed. Chicago, IL: Quintessence Publishing Co; 2012. pp. 133– 58.

148. Tofoli GR, Ramacciato JC, Oliveira PC, Volpato MC, Groppo FC, Ranali J. Comparison of effectiveness of 4% articaine associated with 1:100,000 or 1:200,000 epinephrine in inferior alveolar nerve block. Anesth Prog 2003; 50: 164–8.

149. Sherman MG, Flax M, Namerow K, Murray PE. Anesthetic efficacy of the Gow-Gates injection and maxillary infiltration with articaine and lidocaine for irreversible pulpitis. J Endod 2008; 34: 656–9.

150. Srinivasan N, Kavitha M, Loganathan CS, Padmini G. Comparison of anesthetic efficacy of 4% articaine and 2% lidocaine for maxillary buccal infiltration in patients with irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 107: 133–6.

151. Claffey E, Reader A, Nusstein J, Beck M, Weaver J. Anesthetic efficacy of articaine for inferior alveolar nerve blocks in patients with irreversible pulpitis. J Endod 2004; 3: 568–71.

152. Parirokh M, Yosefi MH, Nakhaee N, Abbott PV, Manochehrifar H. Success rate of bupivacaine and lidocaine as anesthetic agents for inferior alveolar nerve blocks in teeth with irreversible pulpitis. Rest Dent Endod 2015; 40: 155–60.

153. Katyal V. The efficacy and safety of articaine versus lignocaine in dental treatments: a meta-analysis. J Dent 2010; 38: 307–17.

154. Brandt RG, Anderson PF, McDonald NJ, Sohn W, Peters MC. The pulpal anesthetic efficacy of articaine versus lidocaine in dentistry: a meta-analysis. J Am Dent Assoc 2011; 142: 493–504.

155. Dunsky JL, Moore PA. Long-acting local anesthetics: a comparison of bupivacaine and etidocaine in endodontics. J Endod 1984; 10: 457–60.

156. Saatchi M, Farhad AR, Shenasa N, Haghighi SK. Effect of sodium bicarbonate buccal infiltration on the success of inferior alveolar nerve

block in mandibular first molars with symptomatic irreversible pulpitis: a prospective, randomized double-blind study. J Endod 2016; 42: 1458– 61.

157. Hobeich P, Simon S, Schneiderman E, He J. A prospective, randomized, double-blind comparison of the injection pain and anesthetic onset of 2% lidocaine with 1:100,000 epinephrine buffered with 5% and 10% sodium bicarbonate in maxillary infiltrations. J Endod 2013; 39: 597–9.

158. Kreimer T, Kiser R 2nd, Reader A, Nusstein J, Drum M, Beck M. Anesthetic efficacy of combinations of 0.5 mol/L mannitol and lidocaine with epinephrine for inferior alveolar nerve blocks in patients with symptomatic irreversible pulpitis. J Endod 2012; 38: 598–603.

159. Aggarwal V, Singla M, Miglani S, Kohli S, Singh S. Comparative evaluation of 1.8 mL and 3.6 mL of 2% lidocaine with 1:200,000 epinephrine for inferior alveolar nerve block in patients with irreversible pulpitis: a prospective, randomized single-blind study. J Endod 2012; 38: 753–6.

160. Abazarpoor R, Parirokh M, Nakhaee N, Abbott PV. A comparison of different volumes of articaine for inferior alveolar nerve block for molar teeth with symptomatic irreversible pulpitis. J Endod 2015; 41: 1408–11.

161. Fowler S, Reader A. Is a volume of 3.6 mL better than 1.8 mL for inferior alveolar nerve blocks in patients with symptomatic irreversible pulpitis? J Endod 2013; 39: 970–2.

162. Corbella S, Taschieri S, Mannocci F, Rosen E, Tsesis I, Del Fabbro M. Inferior alveolar nerve block for the treatment of teeth presenting with irreversible pulpitis: a systematic review of the literature and meta-analysis. Quintessence Int 2017; 48: 69–82.

163. Fowler S, Reader A, Beck M. Incidence of missed inferior alveolar nerve blocks in vital asymptomatic subjects and in patients with symptomatic irreversible pulpitis. J Endod 2015; 41: 637–9.

164. Parirokh M, Sadr S, Nakhaee N, Abbott PV, Askarifard S. Efficacy of supplementary buccal infiltration and intraligamentary injection to inferior alveolar nerve block in mandibular first molar with asymptomatic

irreversible pulpitis: a randomised controlled trial. Int Endod J 2014; 47: 926–33.

165. Nusstein J, Reader A, Nist R, Beck M, Meyers WJ. Anesthetic efficacy of the supplemental intraosseous injection of 2% lidocaine with 1:100,000 epinephrine in irreversible pulpitis. J Endod 1998; 24: 487–91.

166. Aggarwal V, Jain A, Kabi D. Anesthetic efficacy of supplemental buccal and lingual infiltrations of articaine and lidocaine after an inferior alveolar nerve block in patients with irreversible pulpitis. J Endod 2009; 35: 925–9.

167. Ashraf H, Kazem M, Dianat O, Noghrehkar F. Efficacy of articaine versus lidocaine in block and infiltration anesthesia administered in teeth with irreversible pulpitis: a prospective, randomized, double-blind study. J Endod 2013; 39: 6–10.

168. Rosenberg PA, Amin KG, Zibari Y, Lin LM. Comparison of 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:100,000 epinephrine when used as a supplemental anesthetic. J Endod 2007; 33: 403–5.

169. Singla M, Subbiya A, Aggarwal V et al. Comparison of the anaesthetic efficacy of different volumes of 4% articaine (1.8 and 3.6 mL) as supplemental buccal infiltration after failed inferior alveolar nerve block. Int Endod J 2015; 48: 103–8.

170. Malamed S. The Gow-Gates mandibular block. Evaluation after 4,275 cases. Oral Surg Oral Med Oral Pathol 1981; 51: 463–7.

171. Click V, Drum M, Reader A, Nusstein J, Beck M. Evaluation of the Gow-Gates and Vazirani-Akinosi techniques in patients with symptomatic irreversible pulpitis: a prospective randomized study. J Endod 2015; 41: 16–21.

172. Aggarwal V, Singla M, Kabi D. Comparative evaluation of anesthetic efficacy of Gow-Gates mandibular conduction anesthesia, Vazirani-Akinosi technique, buccal-pluslingual infiltrations, and conventional inferior

alveolar nerve anesthesia in patients with irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 109: 303–8.

173. Goldberg S, Reader A, Drum M, Nusstein J, Beck M. Comparison of the anesthetic efficacy of the conventional inferior alveolar, Gow-Gates, and Vazirani-Akinosi techniques. J Endod 2008; 34: 1306–11.

174. Nuzum FM, Drum M, Nusstein J, Reader A, Beck M. Anesthetic efficacy of articaine for combination labial plus lingual infiltrations versus labial infiltration in the mandibular lateral incisor. J Endod 2010; 36: 952–6.

175. Nusstein J, Lee S, Reader A, Beck M, Weaver J. Injection pain and post-injection pain of the anterior middle superior alveolar injection administered with the Wand or conventional syringe. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004; 98: 124–31.

176. Reader AW, Nusstein JM, Hargreaves KM. Local anesthesia in endodontics. In: Hargreaves KM, Cohen S, eds. Cohen's pathways of the pulp. 10th edn. St Louis, MO: Mosby; 2011. pp. 691–719.

177. Lee S, Reader A, Nusstein J, Beck M, Weaver J. Anesthetic efficacy of the anterior middle superior (AMSA) injection. Anesth Prog 2004; 51: 80–9.

178. Atasoy Ulusoy OI, Alacam T. Efficacy of single buccal infiltrations for maxillary first molars in patients with irreversible pulpitis: a randomized controlled clinical trial. Int Endod J 2014; 47: 222–7.

179. Guglielmo A, Drum M, Reader A, Nusstein J. Anesthetic efficacy of a combination palatal and buccal infiltration of the maxillary first molar. J Endod 2011; 37: 460–2.

180. Aggarwal V, Singla M, Miglani S, Ansari I, Kohli S. A prospective, randomized, single-blind comparative evaluation of anesthetic efficacy of posterior superior alveolar nerve blocks, buccal infiltrations, and buccal plus palatal infiltrations in patients with irreversible pulpitis. J Endod 2011; 37: 1491–4.

181. Moradi Askari E, Parirokh M, Nakhaee N, Hosseini HR, Abbott PV. The effect of maxillary first molar root length on the success rate of buccal infiltration anesthesia. J Endod 2016; 42: 1462–6.

182. Bangerter C, Mines P, Sweet M. The use of intraosseous anesthesia among endodontists: results of a questionnaire. J Endod 2009; 35: 15–8.

183. Walton RE, Abbott BJ. Periodontal ligament injection: a clinical evaluation. J Am Dent Assoc 1981; 103: 571–5.

184. Khedari AJ. Alternative to mandibular block injections through intraligamental anesthesia. Quintessence Int Dent Dig 1982; 13: 231–7.

185. Childers M, Reader A, Nist R, Beck M, Meyers WJ. Anesthetic efficacy of the periodontal ligament injection after an inferior alveolar nerve block. J Endod 1996; 22: 317– 20.

186. Zarei M, Ghoddusi J, Sharifi E, Forghani M, Afkhami F, Marouzi P. Comparison of the anaesthetic efficacy of and heart rate changes after periodontal ligament or intraosseous X-Tip injection in mandibular molars: a randomized controlled clinical trial. Int Endod J 2012; 45: 921–6.

187. Bigby J, Reader A, Nusstein J, Beck M, Weaver J. Articaine for supplemental intraosseous anesthesia in patients with irreversible pulpitis. J Endod 2006; 32: 1044–7.

188. Gallatin J, Reader A, Nusstein J, Beck M, Weaver J. A comparison of two intraosseous anesthetic techniques in mandibular posterior teeth. J Am Dent Assoc 2003; 134: 1476–84.

189. Jensen J, Nusstein J, Drum M, Reader A, Beck M. Anesthetic efficacy of a repeated intraosseous injection following a primary intraosseous injection. J Endod 2008; 34: 126–30.

190. Sixou JL, Barbosa-Rogier ME. Efficacy of intraosseous injections of anesthetic in children and adolescents. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106: 173–8.

191. Van Gheluwe J, Walton R. Intrapulpal injection: factors related to effectiveness. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997; 83: 38–40.

192. Evans G, Nusstein J, Drum M, Reader A, Beck M. A prospective, randomized, double-blind comparison of articaine and lidocaine for maxillary infiltrations. J Endod 2008; 34: 389–93.

193. Smith GN, Smith SA. Intrapulpal injection: distribution of an injected solution. J Endod 1983; 9: 167–70.

194. Newton CW, Coil JM. Effects of age and systemic health on endodontics. In: Hargreaves KM, Berman LH, eds. Cohen's pathways of the pulp. 11th ed. St. Louis, MO: Elsevier Inc. E-books; 2015. Chapter 26, pp. e62–95.

195. DeNunzio M. Topical anesthetic as an adjunct to local anesthesia during pulpectomies. J Endod 1998; 24: 202–3.

196. Kayaoglu G, Gurel M, Saricam E, Ilhan MN, Ilk O. Pre- € dictive model of intraoperative pain during endodontic treatment: prospective observational clinical study. J Endod 2016; 42: 36–41.

197. Ehrmann EH, Messer HH, Adams GG. The relationship of intracanal medicaments to postoperative pain in endodontics. Int Endod J 2003; 36:868–75.

198. Abbott PV. Clinical evaluation, examination and diagnosis of endodontic conditions. In: Ingle J, Rotstein I, eds. Ingle's endodontics, Vol. 1. 7th ed. Raleigh, NC: PMPHUSA, Ltd.; 2016. pp. 215–66.

199. Tupyota P, Chailertvanitkul P, Laopaiboon M, Ngamjarus C, Abbott PV. Supplementary techniques for pain control during root canal treatment of lower posterior teeth with irreversible pulpitis: systematic review and meta-analysis. Aust Endod J 2017: 1–12; https://doi.org/10.1111/aej.12212.

200. Keiser K, Hargreaves KM. Building effective strategies for the management of endodontic pain. Endod Topics 2002; 3: 93–105.

201. Therapeutic Guidelines Ltd. Post-treatment pain management. In: Expert Writing Group – Oral and Dental, eds. Therapeutic guidelines: oral and dental, version 2. North Melbourne, Vic., Australia: Therapeutic Guidelines Ltd; 2012. pp. 127–36.

202. Mehrvarzfar P, Abbott PV, Saghiri MA et al. Effects of three oral analgesics on post-operative pain following root canal preparation: a controlled clinical trial. Int Endod J 2012; 45: 76–82.

203. Parirokh M, Sadr S, Nakhaee N, Abbott PV, Manochehrifar H. Comparison between prescription of regular or on demand ibuprofen on postoperative pain following single visit root canal treatment of teeth with irreversible pulpitis. J Endod 2014; 40: 151–4.

204. Gordon S, Dionne RA, Brahim J, Jabir F, Dubner R. Blockade of peripheral neuronal barrage reduced postoperative pain. Pain 1997; 709: 209–15.

205. Vane JR, Botting RM. The mechanism of action of aspirin. Thromb Res 2003; 110:255-258.

206. Altinoz MA, Korkmaz R. NF-kappaB, macrophage migration inhibitory factor and cyclooxygenase-inhibitions as likely mechanisms behind the acetaminophen- and NSAID-prevention of the ovarian cancer. Neoplasma 2004; 51:239-247.

207. Sudbo J, Reith A. The evolution of predictive oncology and molecular-based therapy for oral cancer prevention. Int J Cancer 2005; 115:339-345.

208. Ahmad N, Grad HA, Haas DA, Aronson KJ, Jokovic A, Locker D. The efficacy of nonopioid analgesics for postoperative dental pain: a meta-analysis. Anesth Prog 1997; 44:119-126.

209. O'Brien TP, Roszkowski MT, Wolff LF, Hinrichs JE, Hargreaves KM. Effect of a non-steroidal anti-inflammatory drug on tissue levels of immunoreactive prostaglandin E2, immunoreactive leukotriene, and pain after periodontal surgery. J Periodontal 1996; 67:1307-1316.

210. Holstein A, Hargreaves KM, Niederman R. Evaluation of NSAIDs for treating post-endodontic pain. Endod Topics 2002; 3:3-13.

211. Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. J Pain Symptom Manage 1999; 18:427- 437.

212. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. N Engl J Med 1994; 331:1675-1679.

213. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal antiinflammatory drugs: nested case-control study. Lancet 2005; 365:475-481.

214. Seymour RA, Meechan JG, Yates MS. Pharmacology and dental therapeutics. 3rd edn. Oxford: Oxford University Press, 1999:92- 93.

215. Therapeutic Guidelines: Analgesics Version 4. Melbourne: Therapeutic Guidelines Ltd. 2002;30-32.

216. Lotsch J, Skarke C, Liefhold J, Geisslinger G. Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. Clin Pharmacokinet 2004; 43:983-1013.

217. Stamer UM, Bayerer B, Stuber F. Genetics and variability in opioid response. Eur J Pain 2005; 9:101-104.

218. Gear RW, Gordon NC, Miaskowski C, Paul SM, Heller PH, Levine JD. Sexual dimorphism in very low dose nalbuphine postoperative analgesia. Neurosci Lett 2003; 339:1-4.

219. Titsas A, Ferguson MM. Impact of opioid use on dentistry. Aust Dent J 2002; 47:94-98.

220. Seymour RA, Meechan JG, Yates MS. Pharmacology and Dental Therapeutics. 3rd edn. Oxford: Oxford University Press, 1999:56-58.

221. Marshall JG. Consideration of steroids for endodontic pain. Endo Topics 2002; 3:41-51.

222. Smith RG, Patterson SS, El-Kafrawy AH. Histologic study of the effects of hydrocortisone on the apical periodontium of dogs. J Endod 1976; 2:376-380.

223. Isett J, Gallatin E, Reader A, Beck M, Padgett D. Effect of intraosseous injection of depo-medrol on pulpal concentrations of PGE2 and IL-8 in untreated irreversible pulpitis. J Endod 2003; 29:268-271.

224. Hargreaves KM, Costello A. Glucocorticoids suppress release of immunoreactive bradykinin from inflamed tissue as evaluated by microdialysis probes. Clin Pharmacol Ther 1990; 48:168-178.