NEUROPATHIC OROFACIAL PAIN : A REVIEW AND GUIDELINES FOR DIAGNOSIS AND MANAGEMENT

E. Russell Vickers Ph.D., M.D.Sc., B.D.S., Grad.Dip.Sc.Med., F.F.P.M.A.N.Z.C.A.

Department of Anaesthesia and Pain Management,

Faculty of Medicine,

University of Sydney.

2001

A treatise submitted for the degree of

Master of Science in Medicine (Pain Management)

Abstract

Neuropathic pain is defined as “pain initiated or caused by a primary lesion or dysfunction in the nervous system”. In contrast to physiological pain that warns of noxious stimuli likely to result in tissue damage, neuropathic pain serves no protective function. Examples of neuropathic pain states include postherpetic neuralgia (shingles) and phantom limb / stump pain. This pain state also exists in the orofacial region, with the possibility of several variants including atypical odontalgia and burning mouth syndrome. There is a paucity of information on the prevalence of neuropathic pain in the orofacial region. One study assessed patients following endodontic treatment and found that approximately 3 to 6% of patients reported persistent pain. Patients predisposed to the condition atypical odontalgia (phantom tooth pain) include those suffering from recurrent cluster or migraine headaches.

Biochemical and neurobiological processes leading to a neuropathic pain state are complex and involve peripheral sensitisation, and neuronal plasticity of the central and peripheral nervous systems. Subsequent associated pathophysiology includes regional muscle spasm, sympathetic hyperfunction, and centralisation of pain. The relevant clinical features of neuropathic pain are: (i) precipitating factors such as trauma or disease (infection), (ii) pain that is frequently described as having burning, paroxysmal, and lancinating or sharp qualities, and (iii) physical examination may indicate hyperalgesia, allodynia and sympathetic hyperfunction. The typical patient complains of persistent, severe pain, yet there are no clearly identifiable clinical or radiographic abnormalities. Often, due to the chronicity of the problem, afflicted patients exhibit significant distress and are poor pain

historians, thus complicating the clinician's task of obtaining a detailed and relevant clinical and psychosocial history.

An appropriate analgetic blockade test for intraoral sites of neuropathic pain is mucosal application of topical anaesthetics. Other, more specific, tests include placebo controlled lignocaine infusions for assessing neuropathic pain, and placebo controlled phentolamine infusions for sympathetically maintained pain. The treatment and management of neuropathic pain is multidisciplinary. Medication rationalisation utilises first-line antineuropathic drugs including tricyclic antidepressants, and possibly an anticonvulsant. Topical applications of capsaicin to the gingivae and oral mucosa are a simple and effective treatment. Neuropathic pain responds poorly to opioid medication. Psychological assessment is often crucial in developing strategies for pain management. Psychological variables include distress, depression, expectations of treatment, motivation to improve, and background environmental factors.

To enable a greater understanding of neuropathic pain, thereby leading to improved treatments, high-performance liquid chromatography-mass spectrometry is one analytical technique that has the potential to contribute to our knowledge base. This technique allows drugs and endogenous substances to be assayed from one sample in a relatively short time. The technique can identify, confirm, and measure the concentrations of multiple analytes from a single sample.

Publications arising from this thesis

Vickers ER, Cousins M. Neuropathic orofacial pain. Part 1: Prevalence and pathophysiology. Australian Endodontic Journal 2000; 26: 19-26.

Vickers ER, Cousins M. Neuropathic orofacial pain. Part 2: Diagnostic procedures, treatment guidelines and case reports. Australian Endodontic Journal 2000; 26: 53-63.

Vickers ER, Cousins M, Nicholas M. Facial pain: a biopsychosocial problem. Medicine Today 2000; 11: 42-8.

Vickers ER, Harris RD. Neuropathic pain as a complication of maxillofacial injury and surgery. Middle East Journal of Oral and Maxillofacial Surgery (in press).

Acknowledgments

I would like to acknowledge my colleagues in the Pain Management and Research Centre, especially Professor Ross Harris, who have been instrumental in helping me to gain a global understanding of the nature of the pain and suffering that occurs in patients afflicted with neuropathic pain. I am also indebted to Professor Michael Cousins and Drs Suellen Walker, Charles Brooker and Allan Molloy who have provided invaluable advice on pharmacological diagnostic tests and therapeutic interventions for the management of neuropathic pain.

I am also grateful to Mr Matt Padula and Associate Professor Kevin Broady, Immunobiology Unit, Department of Cell and Molecular Biology, University of Technology, and Professor Laurence Mather for access to, and training on, high-performance liquid chromatography-mass spectrometry equipment for Chapter 6.

I thank Drs M. Elizabeth Ward and Michael Nicholas, and Professors Michael Cousins, Laurence Mather and Ross Harris who have proof read and contributed material to the publications arising from this thesis. Financial assistance by way of a scholarship from the Department of Anaesthesia and Pain Management, University of Sydney towards the completion of this degree is gratefully acknowledged. Finally, I wish to thank the patients, presented in this thesis and in the relevant publications, for readily giving their permission to use their photos for teaching and educational purposes.

Table of Contents

List of Tables

List of Figures

Abbreviations

AO	atypical odontalgia
CNS	central nervous system
CRPS	complex regional pain syndrome
CT	computerised tomography
Cyclic-AMP	cyclic-adenosine monophosphate
EMLA	eutectic mixture of local anaesthetics
GABA	gamma-aminobutyric acid
GC-MS	gas chromatography-mass spectrometry
HPLC (LC)	high-performance liquid chromatography
IASP	International Association for the Study of Pain
LC-MS	high-performance liquid chromatography coupled to mass spectrometry
MPQ	McGill Pain Questionnaire
MRI	magnetic resonance imaging
MW	molecular weight
NMDA	n-methyl-d-aspartate
NSAIDS	nonsteroidal antiinflammatory drugs
OPG	orthopantomogram
PMRC	Pain Management and Research Centre
PNS	peripheral nervous system
PRI(A)	pain rating index (affective)
PRI(E)	pain rating index (evaluative)
PRI(M)	pain rating index (miscellaneous)
PRI(S)	pain rating index (sensory)
PRI(T)	pain rating index (total)
RCT	root canal therapy
SD	standard deviation
SIP	sympathetically independent pain
SMP	sympathetically maintained pain
TCA	tricyclic antidepressant
TMD	temporomandibular disorder
VAS	visual analogue scale

Glossary of Terms*

after discharge	continued firing of dorsal horn neurons following repetitive peripheral stimulation
algesic	pain producing
algogen	pain producing substance
algogenic	pain producing
allodynia	pain from stimulus that does not normally cause pain
analgetic	pain relieving, analgesic
atypical facial pain**	a diagnosis characterised by vague signs and symptoms with significant psychological factors
atypical odontalgia	severe, throbbing pain without major pathology, phantom tooth pain
central sensitisation	a phenomenon occurring in the dorsal horn and other central structures causing allodynia and secondary hyperalgesia in uninjured tissue surrounding a site of injury
complex regional pain syndrome (CRPS) type I	a syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event
complex regional pain syndrome type II	burning pain, allodynia and hyperpathia usually in the hand or foot, after partial injury to a nerve or one of its major branches
homeopathy (US) / homoeopathy (UK)	a traditional system of diagnosing and treating ailments
hyperalgesia	increased response to a painful stimulus

* Definitions from the International Association for the Study of Pain (IASP), 1994.
** Definition from the IASP, 1986. Term discontinued in 1994.

neuropraxis	crush injury to a nerve
neurotmesis	sectioning or cutting of a nerve
nociception	activation of peripheral nociceptor which is recognised centrally as pain
peripheral sensitisation	a phenomenon where inflammatory mediators sensitise high threshold nociceptors
physiological pain	pain that serves a protective function (as a warning for tissue damage), is transient and well localised
sympathetic hyperfunction	characterised by changes in skin temperature, blood flow, resting sweat output and presence of oedema
sympathetically maintained pain	defined as pain that is maintained by sympathetic efferent innervation or circulating catecholamines
windup	progressive increase in response of dorsal horn neurons due to repetitive peripheral stimulation

CHAPTER 1

Introduction

The physiological purpose of pain is to serve as a warning of actual or potential tissue damage and, consequently, to arouse the organism and initiate withdrawal reflexes to prevent any further tissue damage. The release of putative inflammatory mediators from tissue damage initiates the expression of substances such as nerve growth factor that may cause maladaptive changes such as neuronal sprouting that, in turn, may lead to neuropathic pain. Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" by the International Association for the Study of Pain (IASP) (1).

Causal factors in the development of neuropathic pain include injury, infection and surgery. The emergence of neuropathic pain following dental or maxillofacial injury or surgery / treatment presents an unexpected challenge to the clinician and the patient as it is unlikely to be cured or resolved in the postoperative surgical phase. The expectations of the clinician and patient that a chronic pain condition may develop as a result of injury or surgery can vary depending on the site and severity of injury - for example, patients with back pain are often familiar with the fact that persistent pain and disability may result from a severe back injury. In addition, orthopaedic surgeons are likely to provide sufficient information to the patient concerning the risks and limitations of surgery to cure or alleviate back pain. In contrast, in the area of dental, oral and maxillofacial surgery, patients are

usually well informed about likely functional and aesthetic limitations from treatments (e.g. surgery, implants and reconstruction), but from both the patient's and the clinician's viewpoint, chronic pain is an *unexpected* complication of dental treatment. Consequently, the clinician is left to deal with a patient who has a complication that is complex and multidimensional involving sensory (pathophysiological) and affective (psychological) aspects. Dental or surgical revision for neuropathic pain, unfortunately, is usually contraindicated as there is a high risk of propagating further maladaptive changes in the sensory pathways of the peripheral and central nervous systems.

Neuropathic pain of the oral mucosa and gingivae, and spreading to the face, following dental treatment (usually a dental extraction) has been termed "atypical odontalgia". It has been defined as a "severe throbbing pain in the tooth without major pathology" (1). Documentation of the condition in the dental literature is scarce and accordingly, there is a paucity of information regarding diagnostic and treatment / management procedures. Neuropathic orofacial pain was first described as a painful and unusual condition that occurs in the dentoalveolar structures and oral mucosa (2). Patients reported pain that was moderate to severe in intensity, and with a pattern of referral that may cross the anatomical midline (of the mandible and maxilla) and possibly involve the face. Pain can occur in single or multiple sites (mucosa, extraction sites and remaining teeth). It has also been described as phantom tooth pain due to insufficient information for providing a physiological explanation, and its clinical similarity with phantom limb pain (3, 4). The lack of clinical and

radiographic evidence to establish a diagnosis pertaining to organic pathology gave credence to early investigators that there was a psychogenic basis to the condition (2).

There have been relatively few studies investigating the condition and there is a combined total of less than 200 patients reported in the literature (2, 5, 6, 7, 8). Most of the published reports are epidemiological and there is remarkably little information available for clinicians with respect to diagnostic tests and treatment / management strategies. The aetiology of neuropathic orofacial pain remains poorly understood but the limited data available show that endodontic procedures may account for up to 50% of the cases (9).

The patient afflicted with neuropathic oral / orofacial pain may present to the clinician with a persistent, severe pain without clearly identifiable clinical or radiographic abnormalities. Accordingly, further investigative and curative surgical procedures may be instigated in an attempt to remove the likely anatomical source of the pain. However, the resolution of neuropathic pain does not rely upon surgical intervention but on appropriate pain management strategies. Indeed, where multiple surgical interventions are carried out, the likely outcome is a worsening of the condition. In addition to the clinical challenge of diagnosis and management, the lack of pain relief from previous procedures may cause some patients to display openly negative emotions such as frustration, anger, mistrust and hostility toward clinicians. This is based on patient psychological factors such as their expectations and assurances of cure (pain relief) from surgical intervention. As a consequence of the chronicity of the complaint and the high levels of pain associated with

the condition, there is the possibility of psychological morbidity, and unfortunately, the real potential of suicide in some patients.

A recent review of psychological factors in patients with pain identified a number of crucial points (10):

(i) expectations of surgery to 'fix' the pain, when there is significant background psychological distress, often lead to poor outcomes (11),

(ii) accurate and comprehensible information provided by the surgeon to the patient preoperatively may change the way the patient construes his / her pain, and may reduce the risk of the patient developing postoperative chronic pain (12),

(iii) absence of information, on the other hand, may promote anxiety and fear in the presence of pain (13), and lead to avoidance of normal daily activities (14),

(iv) failure to attend to the patient's fear of pain may interfere with patient's trust of the surgeon and, by a conditioning process, make more likely the rejection of any future surgeon's advice (15, 16).

In the study by Vickers and Harris (10) they concluded that it is essential that the clinician (surgeon) integrates physiological and psychological factors in the pre-, peri- and postoperative phases in order to reduce the potential risks to both the patient and the surgeon.

Historical perspectives

Marbach, Hulbrock, Hohn and Segal (17) suggested that John Hunter, over 200 years ago, was the first to describe neuropathic orofacial pain :

There is one disease of the jaws which seems in reality to have no connection to the teeth, but of which the teeth are generally suspected to be the cause. This deserves to be taken notice of in this place, because operators have frequently been deceived by it, and even sound teeth have sometimes been extracted through an unfortunate mistake.

This pain is seated in some part of the jaws. As simple pain demonstrates noting, a tooth is often suspected, and is perhaps drawn out; but still the pain continues, with this difference, however, that it now seems to be the root of the next tooth; it is then supposed by either the patient or the operator, that the wrong tooth was extracted; wherefore, that in which the pain now seems to be is drawn, but with as little benefit. I have known cases of this kind, where all the teeth of the affected side of the jaw have been drawn out, and the pain continued in the jaw; in others, it has had a different effect, the sensation of pain has become more diffused, and has at last, attacked the corresponding side of the tongue. In the first case, I have known it recommended to cut down upon the jaw, and even to perforate and cauterize it, but all without effect. I have seen cases of some years standing, where the hemlock has

succeeded when the bark has had no effect; but sometimes all attempts prove unsuccessful.

Hemlock and Peruvian Bark, used to treat 'toothache' by Hunter, are still in current use by medical herbalists and homoeopathic practitioners. Hemlock (*Conium maculatum*) is the herb that supposedly caused the death of Socrates by poisoning and is used as a sedative (18), while in the homoeopathic literature it has been used to treat toothache (19). Peruvian Bark (*Cinchona officinalis*) has been used as an antineuralgic remedy in herbal preparations (18). Interestingly, a recent finding in a reprint of an old homoeopathic text first published in 1885 describes the use of capsicum to treat "burning and throbbing pains of the gums" (20). The therapeutic use of capsaicin, the active agent of capsicum, to treat neuropathic pain, a condition that has predominantly burning and throbbing pain qualities, is discussed in a later section of this thesis.

Aims of this treatise

Neuropathic pain has only recently been recognised by dental and medical practitioners as a pain state that deserves urgent understanding. Because of this recent awareness, its epidemiology and pathophysiology are undergoing extensive research in order that preventive measures and effective clinical treatments can become possible. While the majority of this research is directed toward neuropathic pain states associated with medical conditions, there is now a growing recognition in the dental field of the need to investigate orofacial presentations of neuropathic pain. The purpose of this treatise is to review the state of current knowledge of neuropathic orofacial pain and to present appropriate guidelines in its diagnosis and treatment. Accordingly, in this thesis the areas reviewed include the epidemiology, pathophysiology, clinical features, appropriate diagnostic tests,

and pharmacological and psychological strategies of management for neuropathic orofacial pain. A further aim of this thesis is to conduct a preliminary research study using high-performance liquid chromatography-mass spectrometry in order to develop an assay technique (using standards of drug and endogenous substances) that would provide further information toward the understanding, diagnosis and treatment of neuropathic pain.

CHAPTER 2

Prevalence of Neuropathic Pain

Nomenclature

A fundamental requirement for identifying the prevalence of neuropathic pain in society is that clinicians and epidemiologists agree to a uniform classification. Unfortunately, neuropathic pain in the orofacial region has been described with different terminology by various investigators over the years. Originally, the condition was described as atypical odontalgia (AO) in response to the atypical nature of the condition: this term was subsequently listed in the Taxonomy of Chronic Pain Syndromes by the IASP (1). Other terms have included idiopathic odontalgia (21), neurovascular odontalgia (22), and phantom tooth pain (5). More recently, neuropathic pain (oral neuropathic pain / neuropathic orofacial pain) has been the preferred term, and is based on the criteria of the condition's underlying pathophysiology (3, 4, 8, 23). However, it is important to point out that neuropathic orofacial pain is an all embracing term and that several subsets may exist according to the location and aetiology of the neuropathic pain. For example, AO or phantom tooth pain implies pain in the mucosa at the site of a tooth extraction, often with a history of frequent previous restorative and endodontic procedures having been carried out on the tooth in question preceding extraction. Other locations of pain may be the mucosa and gingivae as a result of periodontal therapy, but it is difficult to say whether the pain has arisen in the periodontal tissues from scaling procedures, pulpal stimulation, or both. More

recently, there is preliminary evidence to suggest that burning mouth / tongue syndrome (glossodynia, glossopyrosis) may be another form of neuropathic pain (24).

Prevalence and incidence

The prevalence of neuropathic pain varies according to the site and type of surgery, age of the patient, and co-existing medical conditions. Neuropathic pain is observed in several different medical conditions including postherpetic neuralgia, phantom limb / stump pain, post-spinal cord injury pain and complex regional pain syndromes. The incidence of neuropathic pain varies according to the underlying causal factor. As examples, postherpetic neuralgia occurs in up to 75% of elderly patients with zoster infection but only 10-15% of the younger age group who suffer the condition; between 2-97% of patients may develop post-amputation pain in the limb (phantom limb pain) (25); 60% of patients with traumatic spinal cord injury have pain one year after the event; complex regional pain syndrome type II (previously termed causalgia) occurs in 2-5% of patients after peripheral nerve injury. Other causal factors in the peripheral nervous system (PNS) include malignant invasion of nerves and direct trauma to a nerve such as crush injury (neuropraxis), section or cutting (neurotmesis), or stretch / avulsion. Central nervous system (CNS) trauma, tumour and ischaemia can also be responsible for the development of neuropathic pain.

The incidence of neuropathic pain following surgery is estimated to be 1-2% but probably varies according to the type of operation e.g. increased incidence post-thoracotomy (26). Postoperative neuropathic pain is more prevalent following amputation when there is concurrent pain, and when there has been severe postoperative pain. A review of patients conducted at the author's institution, a multidisciplinary pain centre (Pain Management and Research Centre (PMRC), University of Sydney), revealed that 14% of the patients with neuropathic pain referred to the chronic pain service listed surgery as the causal factor, and that 1-2% of postoperative patients referred to the acute pain service described features of neuropathic pain (C. Hayes, unpublished data, PMRC). In surgical patients, 43% of postmastectomy patients reported recurrent / persistent pain with age being an important variable (65% in the 30-49 year age range, 40% in 50-69 years, and 26% in 70+ years) (25). Postherpetic neuralgia is described as the most common form of neuropathic orofacial pain, identified in 17 patients (0.3%) out of 5,000 patients referred to a medical pain management clinic (9). The incidence of postherpetic neuralgia (all anatomical locations) is 125 per 100,000 of the population (27). In Charcot-Marie-Tooth disease, a hereditary sensori-motor neuropathy, 71% of patients were reported to develop neuropathic pain (28). Not surprisingly, a novel area of research for predicting risks associated with developing chronic pain has focused on the role of genetic factors (29).

No formal prospective studies have been carried out to assess the extent of neuropathic orofacial pain. The only available information consists of several retrospective studies investigating potential causal factors. One study examined the possible role of endodontic

procedures in triggering the condition but was limited in drawing conclusions as it only investigated chronic pain in patients from one endodontist (17). However, the findings at least provide a window regarding the possible extent of the condition. In the study, 732 questionnaires were mailed out to patients who had completed endodontic treatment from one endodontist, with 463 (63%) useable responses. The investigators found 3% of female patients met all four criteria of phantom tooth pain, including no obvious physical or radiographic abnormalities, and 6% manifested three out of four criteria. An interesting aspect of this study, and one that limited the analysis of the problem, was the reluctance of four other endodontists to participate in the study. The non-participating endodontists had remarked, "Perhaps our greatest anxiety, however, is over the fact that a Pandora's box would be opened up." A later publication by the same author (3) extrapolated these earlier findings and suggested that neuropathic orofacial pain (from endodontic procedures) may be present in some 125,000 individuals in the USA alone. In another study that reviewed 118 patients who had completed surgical endodontics, six patients (5%) had persistent pain following surgery, three patients had pain before the surgery but there was no postoperative pain reduction, and three patients developed pain following surgery (30). Other researchers have examined the prevalence of neuropathic pain following dental extractions in patients with frequent headaches (31). In this study, for the cohort with headache (n = 301), pain in the edentate site was reported by 20% of patients suffering from cluster headache and 14% of patients suffering migraine. The authors also found that the more teeth that had been extracted, the greater the pain, and the incidence of neuropathic pain was directly proportional to the number of teeth extracted. In contrast,

there was no patient reporting persistent post extraction pain in the healthy control group (n = 280, no history of recurrent headache). In a cohort of patients with chronic idiopathic orofacial pain, dental therapy was associated with the onset of pain in 28/50 cases (32). Another study analysing patients with chronic orofacial pain (n = 120) revealed that 25% of patients were diagnosed with AO (33).

A potential issue in determining the extent of the problem has been the difficulty faced by various practitioners and investigators in diagnosing pain conditions, or in obtaining a correct diagnosis. For example, one study reported that there was no clearly identifiable cause in 38% of patients in a chronic orofacial pain group (34), and another study of several case reports described patients as having a diagnosis of atypical facial pain (or atypical facial neuralgia), yet these patients clearly fulfilled the description of neuropathic orofacial pain (35). It is plausible that other patients are misdiagnosed, thus underestimating the prevalence of neuropathic pain. A study of a group labelled as chronic idiopathic orofacial pain patients, whose features were suggestive of a diagnosis of neuropathic pain, revealed that 15% of the patients had evidence of post-traumatic stress disorder that coincided with the onset of pain (36).

Psychological factors may well play a part in the development of neuropathic pain through unrealistic expectations of treatment. One report found that 65% of chronic pain patients (back, neck and limb) still had strong beliefs in the possibility of medical cure (including further surgery) for their pain despite an average of 9.7 years of pain and, of these patients,

60% had evidence of overinvestigation and / or overtreatment (37). Thus, in some cases of neuropathic pain, psychological variables may be indirectly responsible for the development of the condition through unnecessary additional treatment that is possibly the direct causal factor. The prevalence of neuropathic orofacial pain has been estimated to be up to 125,000 patients in the USA, perhaps an extraordinary claim (3). However, it should be noted that the majority of people with chronic pain (for example, patients with back pain) do not, in fact, seek extensive investigation and treatment, and there may well be a silent majority of orofacial pain patients as alluded to by Marbach (3).

The reason that patients seek treatment for a chronic pain complaint is complex and multifactorial. It may involve pain relief, by reducing peripheral nociception and sensory aspects of neuropathic pain, altering the perception of pain information in central areas, and it may involve the management of suffering (or psychological distress).

Further prospective studies evaluating the prevalence of neuropathic orofacial pain are warranted. In particular, studies concerning the specific association or development of neuropathic pain from endodontic procedures may prove valuable in a greater understanding of causal factors as a clinical model for medical variants of neuropathic pain.

CHAPTER 3

Neurobiology of Pain: the Progression from the Acute Pain Phase to Chronic Neuropathic Pain

Pain serves as a protective function by providing an early warning of potential tissue damage, thus leading to the initiation of appropriate withdrawal reflexes. 'Physiological pain' is transient and well localised, and the individual can differentiate between pain transmitted by C and A-δ fibres, and touch transmitted by A-β fibres. In addition, pain initiates complex neurohumoral responses that help to maintain homeostasis in acute injury and pain. The response to tissue damage is similar irrespective of the injury such as a surgical incision, traumatic injury (e.g. fracture), soft tissue damage, disease processes (e.g. infection, cancer), and burns. While the degree of trauma and pain may be expected to correlate with the degree of the injury, there is a wide individual variation in the response to an injury, with evidence indicating that both physiological and psychological factors are involved.

While most pain from injury proceeds through an orderly course, there is the potential for the development of vicious cycles of pain. Even a seemingly innocuous stimulus such as a small incision or a tooth extraction may cause a chronic pain state. Unfortunately, there is no accurate technique that can predict those patients who will develop any type of a chronic pain state including neuropathic pain in the orofacial region. Chronic pain is defined as pain that has been present for longer than three months (1). Biological processes

involved in chronic pain may occur within hours to days of an injury, and acute severe pain lasting for only ten days can lead to chronic pain. Events that occur following injury include peripheral sensitisation, and subsequent neuronal plasticity involving the peripheral, central and sympathetic nervous systems. Depending on the severity of trauma, peripheral sensitisation and areas of the CNS may be activated, leading to persistent or pathophysiological pain. The following summary of pain mechanisms is based on a recent extensive review (38).

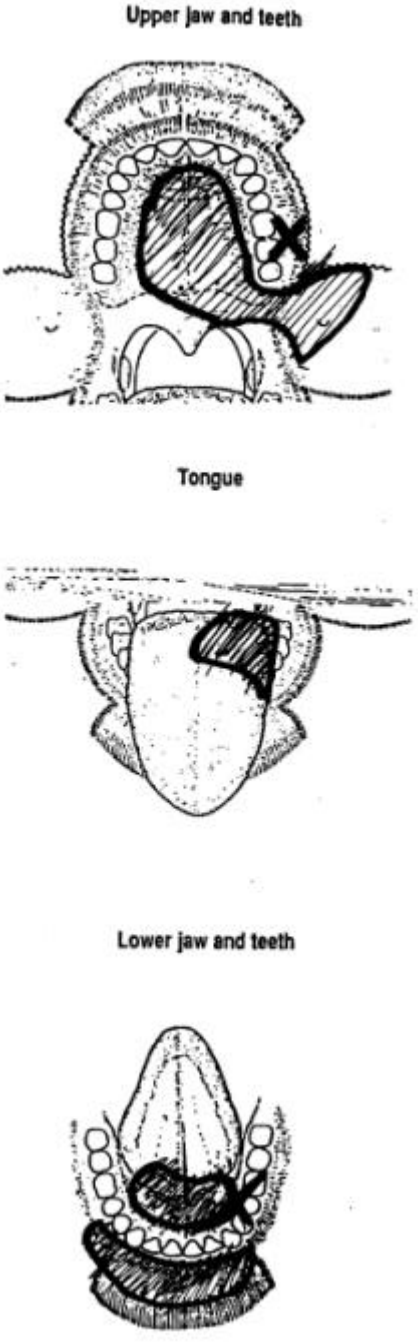
Peripheral sensitisation

An acute injury leads to the Lewis triple response of oedema (wheal), vasodilation (flare) and pain. There is an antidromic response (towards the periphery) along collaterals of primary afferent fibres that results in the local release of chemical mediators to cause an increased response to the noxious stimulus. Nociception primarily involves activation of C fibre afferents by thermal, chemical and mechanical stimuli. The triple response of Lewis describes the sequence of events at the site of injury, and involves the PNS. During inflammation there is a release of intracellular contents from damaged cells and inflammatory cells including macrophages, lymphocytes and mast cells. Nociceptive stimulation also causes the release of peptides such as substance P, neurokinin A and calcitonin gene-related peptide from primary afferent terminals (39). These peptides alter the excitability of nociceptors (and sympathetic fibres), and induce vasodilation and extravasation of plasma proteins, and cause inflammatory cells to release chemical mediators. This produces a ‘sensitising soup’ of inflammatory mediators, including reactive

oxygen species, histamine, cytokines, potassium, serotonin, bradykinin, nitric oxide, leukotrienes, and prostaglandins and enzymes from the cyclooxygenase and lipoxygenase pathways. Following sensitisation, painful stimuli are perceived from low intensity, mechanical stimuli that are not normally painful, a condition termed allodynia (1). Furthermore, hyperalgesia may develop in adjacent tissues, hyperalgesia being defined as an increased response to painful stimuli (1). Noxious skin stimuli sufficiently intense to produce tissue injury usually generate prolonged post-stimulus sensory disturbances including allodynia and hyperalgesia. Hyperexcitability, in part, arises from changes in activity of the spinal cord. Long term consequences of pain thus result from both peripheral and central changes. These changes result in disturbance to the area of injury (primary hyperalgesia) but also to undamaged adjacent areas (secondary hyperalgesia and referred pain) (Figure 1).

Several factors have been demonstrated to be involved in the development of this form of pain (38). First, brief stimulation of peripheral, unmyelinated, afferent fibres can produce substantial and prolonged changes in the cutaneous receptive fields of dorsal horn neurons. The response of dorsal horn neurons can be influenced by the history of previous noxious stimuli. Second, repetitive peripheral stimulation results in a progressive increase in response of dorsal horn neurons, termed windup, and continued firing, termed after discharge. After discharge is four times longer in a

Figure 1. Neuronal plasticity, primary and secondary hyperalgesia, and allodynia. A 62-year-old female with neuropathic pain of ten years duration that demonstrates neuronal plasticity in the form of primary and secondary hyperalgesia, and allodynia. The original site of pain was the extraction of 35, soon followed by 27 (marked X). Primary hyperalgesia is demonstrated by ipsilateral areas on the floor of the mouth and labial mucosa adjacent to 35, and the cheek mucosa and ipsilateral palatal region adjacent to 27. Secondary hyperalgesia is demonstrated on the dorsal surface of the tongue and other regions on the contralateral side.



stimulated, sectioned peripheral nerve compared with an intact nerve. Third, in the presence of an intact nervous system, noxious C afferent fibre input usually does not produce prolonged excitability of the flexion reflex (in rat studies) (40). In contrast, noxious muscle stimulation does produce prolonged changes in the reflex. Consequently, muscle trauma and spasm that can produce local ischaemia and inflammation may cause changes at the spinal level, leading to the development of a vicious cycle of enhanced muscle spasm and progressive increases in pain and the injury response. Fourth, the mechanism of long lasting changes in excitability of spinal neurons is related partially to N-methyl-D-aspartate (NMDA) receptors, with second messengers such as calcium, cyclic AMP and diacylglycerol that trigger prolonged changes. In addition, third messengers such as *c-fos* permit genetic encoding of an altered pattern of enhanced responsiveness of dorsal horn neurons.

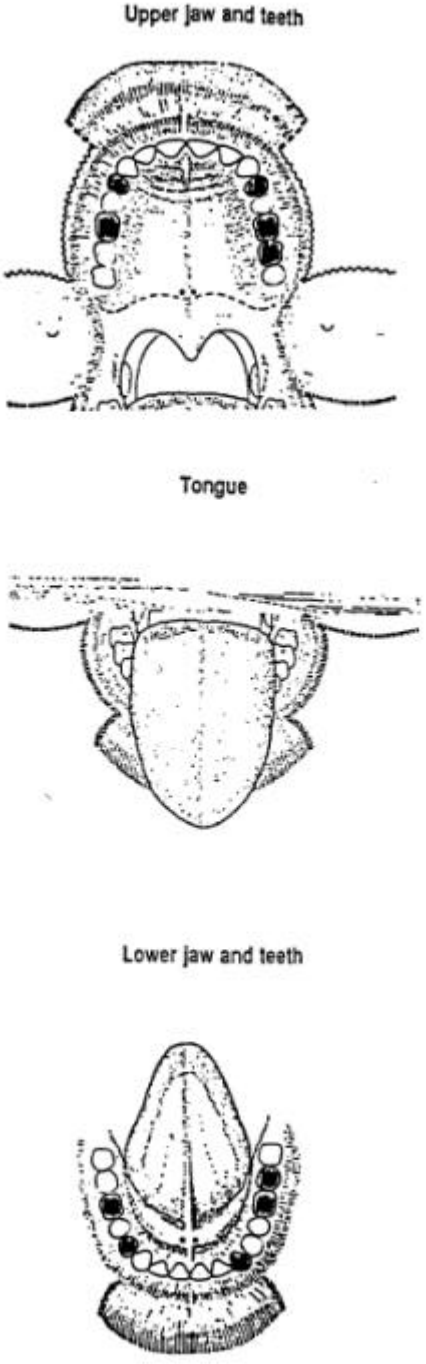
NMDA receptor activation can cause facilitation, windup, central sensitisation, and changes in peripheral fields and induction of oncogenes. At the level of the CNS, neuropathic pain can be seen through a well studied marker, *c-fos* expression. Fos is a protooncogene protein that can be measured by immunoreactivity. It targets genes, leading to genetic changes and subsequent long term responses e.g. to pain. It is induced in spinal cord neurons by noxious stimuli. Innocuous peripheral stimuli can also induce *c-fos* expression, but to a very limited extent; for example, capsaicin administration in an acute inflammation model showed *c-fos* expression to be present for less than 24 hours. In animal studies of pain, inflammation and drug pharmacodynamics (i.e. the effect of the drug

on the body) using rat spinal cord, *c-fos* expression is induced or modulated in various laminae. With peripheral stimulation, the superficial laminae (I-II) of the spinal cord exhibit *c-fos* expression. However, in the case of allodynia in the rat model, the presence of Fos protein in the deeper laminae is elicited, indicating the involvement of A-β afferents (41). *c-fos* activation thus provides important information on possible central mechanisms of neuropathic pain and the potential benefits of preemptive drug treatment. For example, intravenous morphine and morphine administered to the peripheral injury site have been shown to significantly decrease *c-fos* expression from intraplantar carrageenin in the rat. Other drugs demonstrating an effect on the presence of Fos protein include local anaesthetic (lignocaine and bupivacaine), opioid (remifentanil), glucocorticoid (dexamethasone), and nonsteroidal antiinflammatory drugs (NSAIDS) (ibuprofen).

Neuronal plasticity

Pathophysiological pain such as neuropathic pain can be explained, in part, by nervous system plasticity. Patients with neuropathic orofacial pain often describe multiple sites of pain in teeth across all quadrants although the initiating event has been a dental procedure in a single tooth (Figure 2). Neuroplasticity may also occur at the peripheral and / or spinal cord level; for example, damaged nerve fibres may produce neuromas. Nerve growth factor, a peptide that regulates neuronal growth, is a prime initiator of nerve sprouting that is involved in neuroplasticity and may play a role in altering responsiveness to sensory input. Peripheral abnormalities can result from sensitisation of nociceptors or axon damage, permitting ectopic locations for

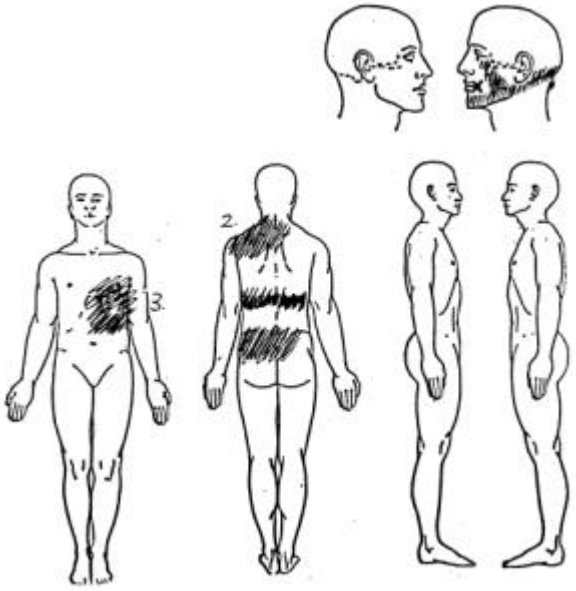
Figure 2. Multiple sites of pain in teeth demonstrating neuronal plasticity. A 45-year-old female with neuropathic orofacial pain of 18 months duration. The intraoral pain map indicated multiple sites of pain in teeth in both (a) maxilla, and (b) mandible, that had no radiographic or clinical pathology.



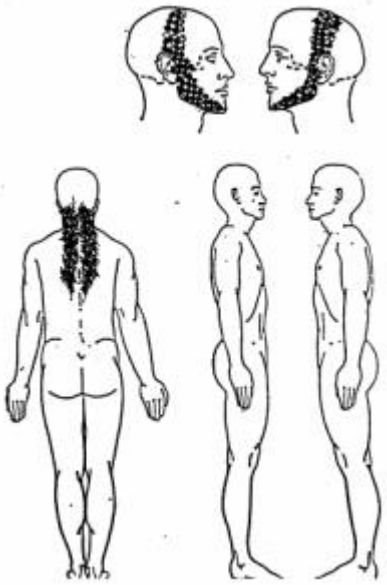
spontaneous neuronal discharge (peripheral neuromas). These changes may also occur along the course of axons and produce microneuromas. Neuromas are capable of spontaneous discharge, greatly enhanced and prolonged discharges, and show minimal accommodation. Properties of neuromas include sensitivity to mechanical stimuli, spontaneous firing and sensitivity to noradrenaline. The sensitivity of neuromas appears to be related to the time since nerve injury, being most intense within the first two weeks of neuroma formation, but then maintained at a lesser, continued level. Clinically, this situation is recognised by the production of intense, electric, shock-like pain at the site of the neuroma, and radiating pain on percussion of the neuroma (Tinel's sign). Damage to axon sheaths may also result in demyelination, resulting in nerve hyperexcitability. This causes paroxysms of pain and afferent activity may initiate reflex motor activity causing muscle spasm. This may account for the development of a temporomandibular disorder (TMD) that is secondary to the primary neuropathic oral pain (Figure 3). Evidence has shown that peripheral neuroma pain may not be blocked by local anaesthetic at the site, suggesting that central mechanisms are involved (42). In the clinical situation of patients with neuropathic oral pain there is a wide range of responses to topical anaesthetic application, with patients demonstrating either complete, partial or no pain reduction to somatosensory blockade (43, 44). Evidence from animal studies suggests that there is a genetic predisposition in the development of spontaneous activity in neuromas. In the clinical situation, patients who develop neuromas frequently have similar problems after attempts to remove them (42).

Figure 3. Development of temporomandibular disorder secondary to neuropathic pain in two patients: (a) myofascial pain was initially restricted to the left masseter muscle and over the course of several years it spread to involve the left shoulder, lower thoracic and lower lumbar / sacral regions, (b) description of neuropathic intraoral pain of three years duration with subsequent involvement of masseter, temporalis and semispinalis capitis muscles.

(a)



(b)



In summary, the latter stages of injury involve invasion of the damaged area by phagocytes and fibroblasts. Damaged nerve endings and capillaries sprout and infiltrate into the area where sensory, sympathetic and motor fibres are already present. C fibres are involved in detecting the altered chemical environment, a phase that coincides with the beginning of scar formation, and the patient's probable awareness of a persistent pain problem.

Sympathetically maintained pain

Another development in neuropathic pain may be abnormal, ongoing sympathetic activity, termed sympathetically maintained pain (SMP). SMP is defined as pain that is maintained by sympathetic efferent innervation or by circulating catecholamines. The pathophysiology of SMP probably involves coupling between sympathetic and somatosensory pathways. This has been postulated to occur at peripheral nociceptors, at the dorsal root ganglion with subsequent sprouting of noradrenergic perivascular axons, and at central spinal cord sites. Both direct and indirect methods of excitation of peripheral nociceptors by noradrenaline have been proposed (45). Following nerve damage or chronic inflammation, a subset of C-polymodal nociceptors has been shown to develop sensitivity to sympathetic stimulation, and thus, may be directly stimulated by noradrenaline. Alternatively, noradrenaline may act indirectly via release of prostaglandins that, in turn, sensitise the nociceptor. Inflammation may also induce nociceptor sensitivity to noradrenaline. In considering endodontic and other dental procedures, the practitioner should be aware of the possibility, or indeed the likelihood, of preexisting gingival / periodontal / periapical

inflammation and the potential for the interaction of noradrenaline in dental anaesthetic cartridges.

SMP may also involve central mechanisms that could explain the development of hyperalgesia and more generalised pain. Pain transmission pathways may undergo plasticity through changes in receptor sensitivity, genetic changes and neuroanatomical reorganisation, leading to central sensitisation and windup. C-polymodal nociceptors can activate and sensitise wide dynamic range neurons; these then respond to activity in large diameter A-mechanoreceptors that are activated by light touch. The pain threshold is reduced, and previous subthreshold stimuli are then perceived as painful (i.e. hyperalgesia). This explains the frequent observation in neuropathic oral pain patients that they cannot tolerate wearing a denture following extraction, particularly where the denture saddle rests upon an area of allodynia or hyperalgesia.

There is now an increased awareness of the role of the sympathetic nervous system in a variety of neuropathic pain states such as postherpetic neuralgia, CNS lesions and amputation (phantom pain) syndromes (46). SMP has been linked in the past with reflex sympathetic dystrophy and causalgia, now designated Complex Regional Pain Syndromes (CRPS) types I and II, respectively. CRPS is a clinical diagnosis that may include, but does not imply, an underlying component of SMP. The main feature of CRPS is pain (with associated allodynia / hyperalgesia) that is disproportionate in severity to the inciting event and occurs in a regional distribution beyond the territory of a single peripheral nerve. In

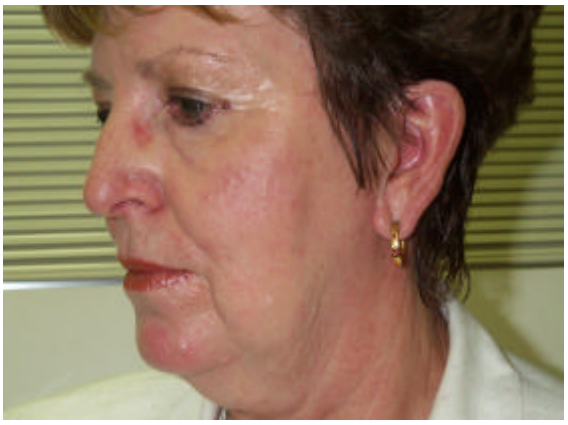
CRPS there may be associated oedema, changes in blood flow, abnormal sudomotor activity such as sweating, and motor dysfunction (Figures 4, 5). The present IASP taxonomy does not include a category for CRPS type I involving orofacial locations; however, there is clear clinical evidence of sympathetic nervous system involvement in neuropathic orofacial pain (Figures 4, 5) (8, 9). Although SMP may be a component of the patient's pain syndrome, it is often impossible to predict and distinguish, on the basis of presenting symptoms alone, those who will benefit from sympatholytic procedures (47).

Gender issues in pain in the orofacial region

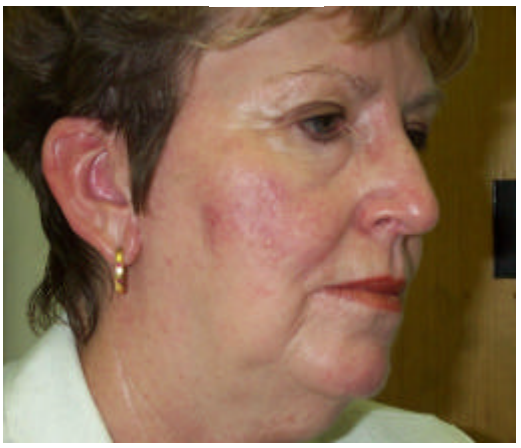
Numerous factors are thought to play a pivotal role for gender differences in patients with pain (48), particularly the greater prevalence of women with orofacial pain conditions that appears to involve neurobiological and psychological aspects. It has been reported that there is a significantly greater prevalence of women (88:32) with chronic orofacial pain presenting at a pain management centre (33). Specifically, those patients with pain of idiopathic onset and marked psychosocial variables (previously termed atypical facial pain) were significantly higher (34:6). For a group diagnosed with neuropathic orofacial pain (including atypical odontalgia) the female : male ratio was 34:16 (8). In comparison, the female : male ratio of general body pain conditions such as back pain and phantom limb pain at the same institution was 45:55. Women report more multiple or recurrent pains than men, particularly more at certain ages and certain body regions (49). In,

Figure 4. Sympathetic hyperfunction secondary to neuropathic pain. A 58-year-old female with neuropathic pain on the right side of the face after dental treatment in the right maxilla: (a) left side of face with normal complexion (b) sympathetic hyperfunction (redness) in the right cheek region “nearly always present and needs cosmetic applications to mask it”, (c) frontal photograph for comparison.

(a)



(b)



(c)

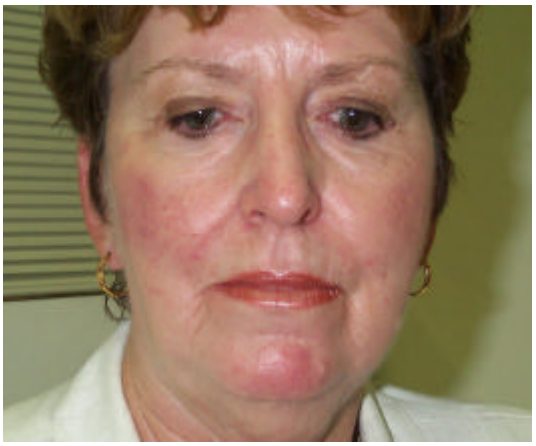
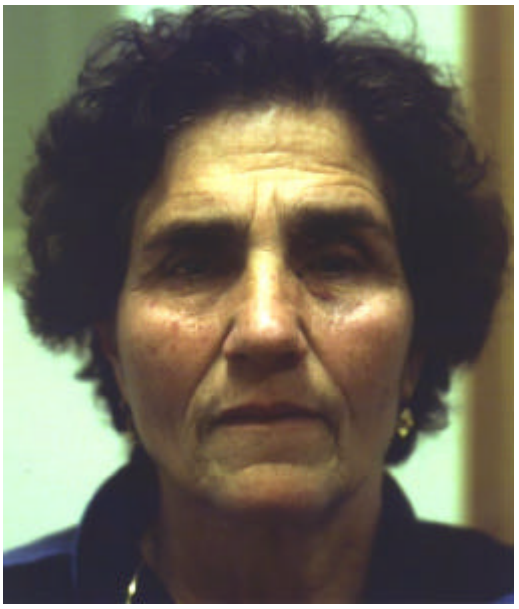
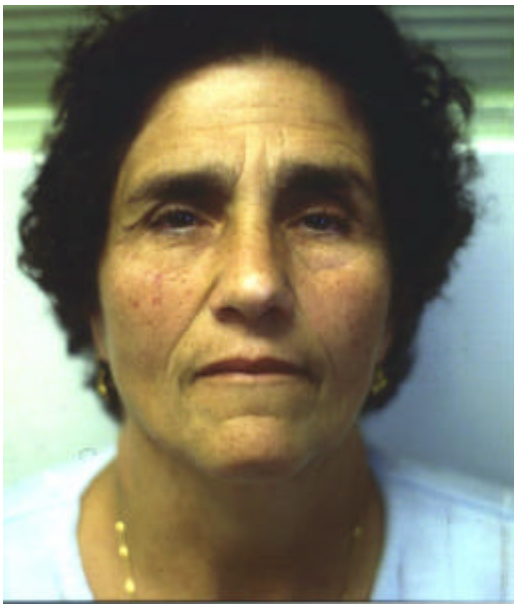


Figure 5. Recurrent sympathetic nervous system involvement. A 55-year-old female patient with a three year pain history: (a) normal facial appearance, (b) episode of sympathetic nervous system involvement characterised by swelling and an increase in pain intensity in the left cheek region. There is a noticeable loss of the left nasolabial crease that persisted for several days.

(a)



(b)



particular, there is an increased prevalence of recurrent or chronic pain syndromes in the head and neck region for females compared with males (Table 1) (50).

Gender differences exist in pain intensity in acute orofacial pain. In a third molar surgical extraction study females reported higher baseline pain ratings than males (average visual analogue scores of 7 and 4.7, respectively), but administration of kappa-opioid agonists (nalbuphine, butorphanol) produced significantly greater pain relief and a longer duration of action for females than males (51). In contrast, in the chronic situation, there is no significant difference in pain intensity for gender as measured by numerical rating scales and the McGill Pain Questionnaire (33). A possible explanation may be found in oestrogen concentrations. Oestrogen is known to modulate opioid mechanisms by increasing endogenous opioid activity (52) and to regulate central expression of nerve growth factor (53), both important mechanisms in the development of neuropathic pain.

Psychological differences in the expectation of pain also exist. Male children have been shown to underestimate, and female children overestimate, the expected pain of impending venepuncture, yet pain ratings were similar for the actual procedure (54). In a study assessing psychological variables in patients with osteoarthritis, there were significant differences in pain, pain behaviour, and physical disability between men and women. Women had significantly higher levels of pain and physical disability,

Table 1. Prevalence of recurrent or chronic pain syndromes in the orofacial, and head and neck region (modified from Berkley KJ, Holdcroft A. Sex and gender differences in pain. In: Wall PD, Melzack R, eds. Textbook of Pain, 4th ed. London, Churchill Livingstone, 1999, p. 952) (50).

Female prevalence	**Male prevalence**	**No sex prevalence**
migraine with aura	migraine without aura	acute tension headache
chronic tension headache	cluster headache	maxillary sinusitis
cervicogenic headache	post traumatic headache	acute pulpitis
trigeminal neuralgia		cracked tooth syndrome
temporomandibular disorder		dry socket
occipital neuralgia		
periodontitis		
atypical odontalgia		
burning mouth / tongue syndrome		
carotidynia		
chronic paroxysmal hemicrania		
temporal arteritis		

and exhibited more pain behaviour than men. However, once catastrophising was entered into the analyses, the previously significant effects of gender were no longer found (55). Females and males may not interpret and report sensations in the same way and, subsequently, there may be gender differences in the way men and women communicate with the surgeon regarding their pain, hurt and suffering. In summary, hormonal, neurobiological and psychological (learned) factors have important roles in gender differences. Further research into gender is warranted to understand these differences, and specifically for the area of orofacial pain.

Summary of features that suggest neuropathic pain

(modified from the National Health and Medical Research Council. Acute Pain Management: Scientific Evidence. AusInfo, Canberra. 1998; pp. 11-12) (56).

- Pain in the absence of ongoing tissue damage
- Pain in an area of sensory loss
- Paroxysmal or spontaneous pain
- Allodynia, hyperalgesia and dysaesthesia
- Delay in onset of pain following injury or surgery of weeks or months (NB some neuropathic pain has immediate onset)
- Poor analgetic response to opioids

CHAPTER 4

Diagnostic Procedures and Treatment Guidelines

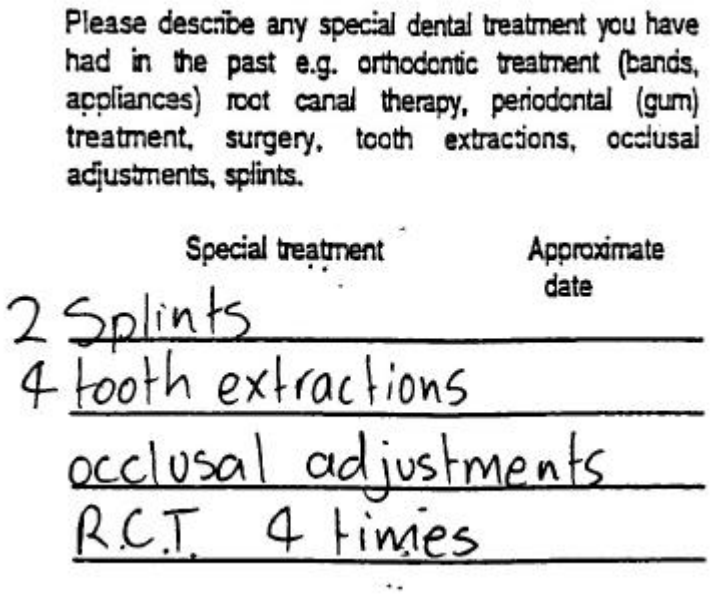
A correct diagnosis for patients with neuropathic pain is vital for administering the appropriate treatments and management strategies. Factors contributing to chronic pain fall into three broad categories: nociceptive, neuropathic and psychological / environmental. It is imperative to diagnose which category (or categories) of pain the patient presents with, because the treatments vary. Furthermore, the large majority of patients may display multiple co-existing factors. For example, a patient with neuropathic pain may have significant psychosocial factors modulating the pain, and then, in addition, have nociceptive pain from surgery performed in an attempt to 'cure' the existing pain. Nociceptive factors result from stimulation of nociceptors by tissue damaging (noxious) stimuli where the nervous system is intact, such as early dental infection / pulpitis. Neuropathic pain results from damage, disease, or complete section (deafferentation) of the PNS or CNS in the absence of a peripheral noxious stimulus. Psychosocial and / or environmental factors may predominate when no detectable noxious stimulus or damage to the nervous system is present and pain behaviour is presumed to arise primarily from these factors.

A patient with chronic pain may develop, in addition to his / her current complex biopsychosocial problem, further problems such as myofascial pain (57). In particular, in the case of neuropathic orofacial pain, it is likely that two out of three patients will develop

a secondary TMD (8). Iatrogenic causes may play an important role in the further development of neuropathic orofacial pain (Figure 6). For example, a dental practitioner may provide treatment in a tooth or site of pain where there is no obvious clinical or radiographic abnormality, thereby aggravating any resident neuropathic pain problem.

Neuropathic pain is often reported by patients to be severe, and can be accompanied by significant levels of distress. Moreover, the impact of the pain is not confined solely to the afflicted patient. The scope of changes attributed to chronic pain includes lost work productivity, reduced levels of social activities, and behavioural changes in the patient, spouse and family (Figure 7). It is now well recognised that early intervention can play a major role in achieving more successful outcomes for patients. The basis of early intervention with its appropriate treatment(s) relies on a correct and early diagnosis utilising validated methods and tests. In addition, the prognosis of neuropathic orofacial pain is dependent on curtailing the traditional Cartesian approach to painful sites where the concept is that the removal or amputation of the suspect site (tooth) will lead to the resolution of the pain (Figure 6). This approach causes further iatrogenic problems by worsening the patient's current (neuropathic) pain problem. Moreover, the development of a TMD secondary to the neuropathic pain occurs through neuronal circuits and the unnecessary extraction of teeth with a resultant malocclusion.

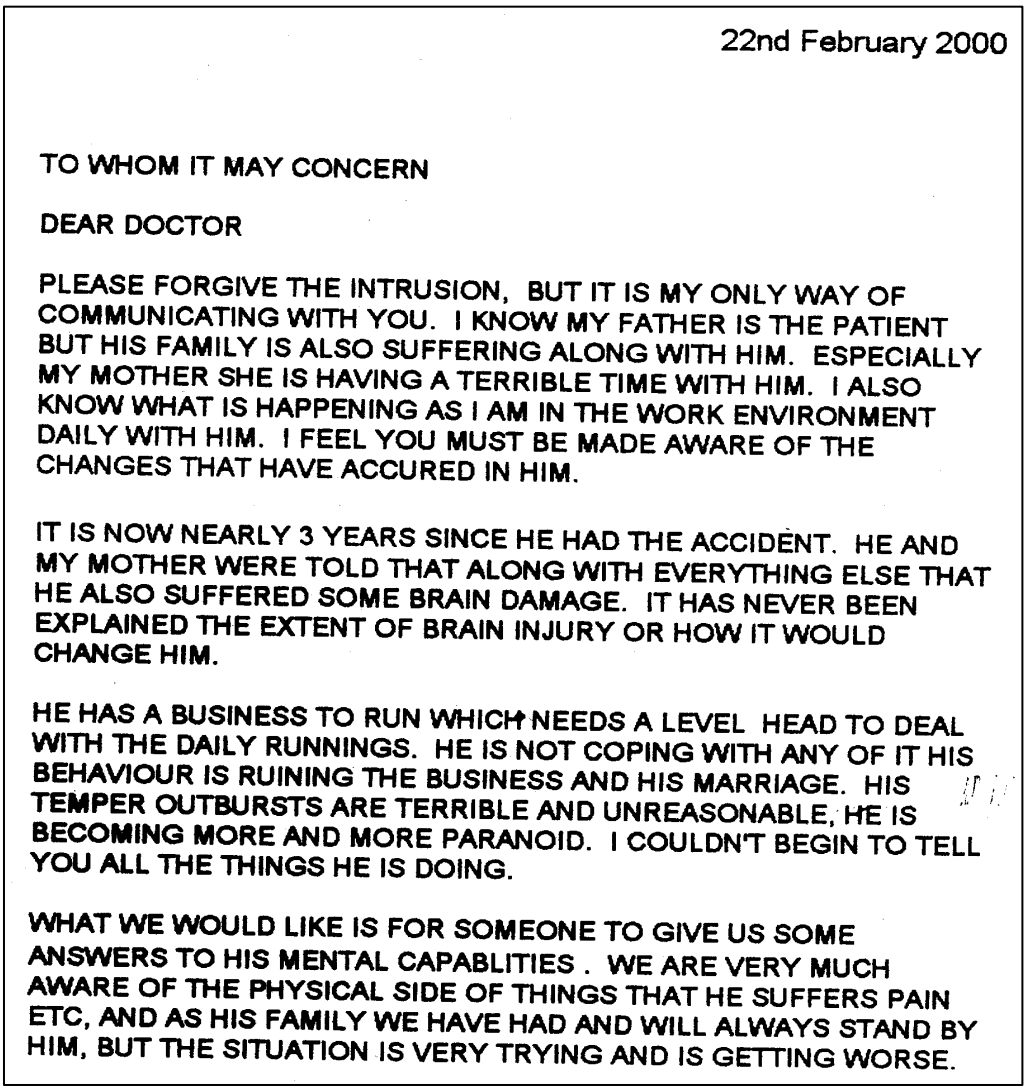
Figure 6. Iatrogenic dental procedures in a patient with neuropathic pain. A 33-year-old female patient with a three year history of neuropathic pain reporting her compilation of dental procedures (n > ten procedures) carried out by several dentists over a nine month period to 'cure' the pain.



Please describe any special dental treatment you have had in the past e.g. orthodontic treatment (bands, appliances) root canal therapy, periodontal (gum) treatment, surgery, tooth extractions, occlusal adjustments, splints.

Special treatment	Approximate date
2 Splints	
4 tooth extractions	
occlusal adjustments	
R.C.T. 4 times	

Figure 7. Effects on the family of a patient with neuropathic pain. Letter sent by family member (patient's daughter) detailing the range of effects on the family and business.



22nd February 2000

TO WHOM IT MAY CONCERN

DEAR DOCTOR

PLEASE FORGIVE THE INTRUSION, BUT IT IS MY ONLY WAY OF COMMUNICATING WITH YOU. I KNOW MY FATHER IS THE PATIENT BUT HIS FAMILY IS ALSO SUFFERING ALONG WITH HIM. ESPECIALLY MY MOTHER SHE IS HAVING A TERRIBLE TIME WITH HIM. I ALSO KNOW WHAT IS HAPPENING AS I AM IN THE WORK ENVIRONMENT DAILY WITH HIM. I FEEL YOU MUST BE MADE AWARE OF THE CHANGES THAT HAVE ACCURED IN HIM.

IT IS NOW NEARLY 3 YEARS SINCE HE HAD THE ACCIDENT. HE AND MY MOTHER WERE TOLD THAT ALONG WITH EVERYTHING ELSE THAT HE ALSO SUFFERED SOME BRAIN DAMAGE. IT HAS NEVER BEEN EXPLAINED THE EXTENT OF BRAIN INJURY OR HOW IT WOULD CHANGE HIM.

HE HAS A BUSINESS TO RUN WHICH NEEDS A LEVEL HEAD TO DEAL WITH THE DAILY RUNNINGS. HE IS NOT COPING WITH ANY OF IT HIS BEHAVIOUR IS RUINING THE BUSINESS AND HIS MARRIAGE. HIS TEMPER OUTBURSTS ARE TERRIBLE AND UNREASONABLE, HE IS BECOMING MORE AND MORE PARANOID. I COULDN'T BEGIN TO TELL YOU ALL THE THINGS HE IS DOING.

WHAT WE WOULD LIKE IS FOR SOMEONE TO GIVE US SOME ANSWERS TO HIS MENTAL CAPABLITIES . WE ARE VERY MUCH AWARE OF THE PHYSICAL SIDE OF THINGS THAT HE SUFFERS PAIN ETC, AND AS HIS FAMILY WE HAVE HAD AND WILL ALWAYS STAND BY HIM, BUT THE SITUATION IS VERY TRYING AND IS GETTING WORSE.

Consequently, specific diagnostic tests are crucial to engage early interventional treatments and to avoid iatrogenic spread of the pain.

Recommended diagnostic procedures

1. *Pain history*

In addition to a routine medical history and clinical examination, there is the need to obtain specific information in relation to a pain history. Pain maps are useful to delineate the origin of the pain and subsequent areas of radiation. The following information should be sought in a pain history based on the National Health and Medical Research Council guidelines for pain management (56):

- Circumstances associated with pain onset
- Primary site of pain
- Radiation of pain
- Character of pain
- Intensity of pain (at rest, at present, during last week, highest level)
- Factors altering pain (what makes it worse, what makes it better)
- Temporal quality (continuous, periodic, intermittent)
- Effect of pain on activities
- Effect of pain on sleep
- Medications taken for pain
- Other treatments used for pain
- Health professionals consulted for pain treatment

- Patient's knowledge, expectations and preferences for pain management
- Patient's beliefs as to the cause of the pain
- Reduction in pain required to resume reasonable activities
- Presence of depression, anxiety or psychiatric disorder
- Family expectations
- Ways the patient describes or shows the pain

2. Pain measuring instruments

The visual analogue scale (VAS) is a simple, pencil and paper instrument that is used by the patient to quantitate pain intensity. In addition, the VAS can be incorporated into daily pain intensity log charts to view the efficacy of a diagnostic or treatment trial. Analogue scales have been shown to demonstrate reliability, validity and versatility (58). Variations of the VAS exist and a comparison of analogue scales has revealed that graded numerical rating scales (NRS) are more reliable than descriptive analogue scales (59). An evaluation of various length and end-phrase variations of the VAS has shown that the ten cm VAS exhibits the smallest measurement error, while the end-phrase "worst pain imaginable" provides the greatest sensitivity in measuring present pain in patients with dental pain (60). The VAS is useful for both chronic and experimental pain (61).

The description of a pain condition (i.e. the patient's choice of words applicable to the qualities of the pain condition) can provide simple but valuable information for diagnosis, selection of appropriate drugs, and levels of psychological distress. The MPQ is another

pencil and paper pain measuring instrument that allows the patient to select appropriate pain word descriptors. It can measure pain intensity through various indices including sensory and affective components of pain. The MPQ has been used for evaluating acute (postoperative) orofacial pain from third molar surgery (62). In addition, the MPQ has been used to assess acute toothache patients and was able to differentiate different stages of pulpitis (irreversible versus reversible), with a correct prediction rate of 73% in subjects (63). Similar findings have been reported in using the MPQ to differentiate pulpitis from pericoronitis (64). One study assessed the utility of the MPQ for analysing chronic orofacial pain conditions; two chronic orofacial pain conditions were examined, atypical facial pain and trigeminal neuralgia, and the authors correctly predicted the diagnosis in 90% of patients (65). The MPQ has a standard form that was designed by Melzack (66) and the form consists of 78 words categorised into 20 groups, representing the four major dimensions of pain quality: sensory, affective, evaluative and miscellaneous pain descriptors. These groups of words are scored and ranked to furnish four indices of pain quality; pain rating index of sensory descriptors (PRI(S)), pain rating index of affective descriptors (PRI(A)), pain rating index of evaluative descriptors (PRI(E)) and the pain rating index of miscellaneous descriptors (PRI(M)). The four pain rating scores can then be added to give a fifth index, the total pain rating index (PRI(T)).

3. Local anaesthetic techniques

A positive response (pain reduction) to somatosensory blockade of pain sites by various routes of administering local anaesthetic agents is suggestive of neuropathic pain (and

nociceptive pain). In the orofacial region, the area can be tested by several techniques to determine possible sources of the location of pain. Ideally, these local anaesthetic agent techniques should be employed in a controlled, patient blinded manner, i.e. incorporating the use of placebo injections (placebo responses occur in up to 60% of patients with neuropathic pain). First, the administration of a topical anaesthetic to mucosal pain sites is advantageous by being non-invasive, with a study revealing that 37/38 patients with neuropathic pain responded with a reduction in pain when a topical anaesthetic cream was applied for five minutes (8). The topical anaesthetic of choice is EMLA cream 5% (AstraZeneca, Sydney, Australia) which is a eutectic mixture of lignocaine and prilocaine bases. The eutectic mixture has a low melting point of 17^0C and is an oil at mouth temperature, thus facilitating absorption. The agent has been shown to have rapid oral mucosal absorption, to penetrate deeply into the oral tissues, and to be safe from toxicity from extended application times of up to 30 minutes (67, 68). It is superior for sensory blockade compared with lignocaine 5% and 10% ointments (Xylocaine 5% and Xylocaine 10% Special Adhesive) and a benzocaine / amethocaine mixture (NUM) (67). The technique involves obtaining a VAS for basal pain intensity, followed by the removal of excess saliva from the test site using fresh cotton gauze. Isolation and placement of a placebo such as petroleum jelly on a cotton bud for five minutes follows, and another VAS is obtained. The placebo is then wiped off and a liberal quantity (1 g) of EMLA applied for five minutes and a final VAS measured. The VAS responses can then be assessed to determine comparative pain reduction with EMLA.

Further local anaesthetic blockade can then be used to confirm other possible locations of peripheral neuropathy. This should be performed with sequential proximal anatomical blocks. For example, in testing the mandibular canine region, the analgetic sequence would be EMLA, mental nerve block, mandibular block using the 'conventional' technique blocking the mandibular nerve at the mandibular foramen, then a high mandibular block using either the closed mouth or Gow-Gates techniques (69, 70). The Gow-Gates block has been shown to be more effective for producing analgesia but the closed mouth technique, also termed the Akinosi block (71), is a more acceptable technique to patients according to reports (72). This provides potentially valuable information as to the location of any neuroma formation, and thus the likely success of utilising topical antineuropathic agents such as capsaicin. Obviously, in the situation of a patient who is a non-responder to all blocks, there is the likelihood of CNS changes (centralisation of pain). Hypothetically, the probable selection of plain lignocaine (1-2%) as the test agent is preferable to lignocaine with vasoconstrictor (adrenaline / noradrenaline combinations) because of the potential for noradrenaline and protons (low pH of solution) to actually increase pain before the onset of neural blockade from lignocaine in the dental anaesthetic cartridge.

Three types of patient blinded, controlled local anaesthetic techniques are available. The first technique involves using normal saline as a control agent followed by a local anaesthetic agent such as plain lignocaine (1-2%), obtaining VAS measures at baseline (prior to saline injection), five minutes after the saline block, and five minutes after the local anaesthetic block. The second technique is more robust and utilises two local anaesthetics

with different systemic absorption rates. The first block utilises plain lignocaine, then at a later stage, plain bupivacaine (0.025-0.5%). Bupivacaine has a slower absorption rate than lignocaine and a positive response would show pain reduction with both agents, but a longer period of pain reduction using bupivacaine. A third, superior technique, if time permitted, would employ triple patient blinded blocks: the first injection using normal saline, the second using plain lignocaine, and the third using plain bupivacaine.

The intravenous lignocaine test requires referral to a specialist pain clinic with the services of an anaesthetist / pain specialist. This test has been reported to be useful in discriminating neuropathic pain from other forms of chronic pain (73). The test involves an infusion of lignocaine in increments up to a maximum of 2 mg/kg. It is placebo controlled and only one study has tested its application for neuropathic orofacial pain. In a test group of eight patients, 50% had a positive response with an average pain reduction of 68±10%. Interestingly, all the negative responders had a history of endodontic therapy in the area of pain but no further details were reported by the investigators to draw conclusions (73).

4. Sympathetic procedures

A thorough clinical history can identify those patients with a component of SMP. Clinically, the patient may give a history of episodes of oedema involving the face, and occasionally with a hot or burning quality. The clinician should ask the patient whether or not he /she experiences episodes of swelling in the face. An affirmative response warrants referral for more definitive tests such as the phentolamine infusion.

A diagnosis of SMP is made when the pain is relieved by sympathetic blockade. However, there is no single test with adequate sensitivity and selectivity to distinguish SMP from sympathetically independent pain (SIP). The sympathetic chain receives efferent preganglionic fibres from the ventral roots of T1 (first thoracic nerve root) to L2 (second lumbar nerve root) and forms the stellate ganglion, thoracic paravertebral chain, coeliac plexus, lumbar paravertebral chain and superior hypogastric plexus. The sympathetic supply in the orofacial region originates from the stellate ganglion located in the neck. Studies using thermography (74, 75) and stellate ganglion block (9) have implicated SMP as occupying a role in neuropathic orofacial pain. Stellate ganglion block has been used as a diagnostic test for SMP in head, neck and upper limb (76). However, limitations of stellate block include false positive responses (spread of local anaesthetic to somatic fibres), false negative responses (incorrect placement of local anaesthetic), and an inability to conduct blinded, placebo controlled injections (47). The intravenous administration of phentolamine (α-1 and α-2 adrenoceptor antagonist) has been utilised as a diagnostic test for SMP and a positive response (pain relief) may be predictive of the success of a subsequent series of sympathetic blocks (77). In addition, the phentolamine test has the advantages of being less invasive and less painful, and blinded, placebo controlled infusions can be administered. A specialist anaesthetist must perform the test and patients are monitored with electrocardiography, pulse oximetry, and non-invasive blood pressure. The test involves the initial administration of 500 mL of intravenous normal saline (0.9%) to limit potential hypotension from phentolamine. VAS scores are recorded at baseline and at five

minute intervals. During the trial, a saline placebo is infused over ten minutes followed by phentolamine 15 mg over ten minutes. If no analgetic response is reported by the patient and cardiovascular side effects are minimal (tachycardia and hypotension), further 5 mg bolus doses of phentolamine can be administered until a response is observed (pain relief or side effects). Only one study has employed the saline / phentolamine test to evaluate the sympathetic contribution to neuropathic orofacial pain with results showing that there was a significant response to the phentolamine challenge when 75% of patients (9/12) claimed a reduction (wide variation) in pain intensity ratings (8).

The involvement of SMP can be assessed by measuring sympathetic hyperfunction through changes in skin temperature (thermography and thermometry), blood flow (cutaneous Doppler), resting sweat output and the presence of oedema. Electronic thermography has been suggested to be useful for SMP, although it is not a readily available test (75). However, the technique is promising because it is non-invasive and is selective in thermal accuracy (100%), with results showing the affected (painful) side of the face to be hotter than the non-painful side (range 0.4-3.1^{0}C, mean = 1.1±0.8, n = 10).

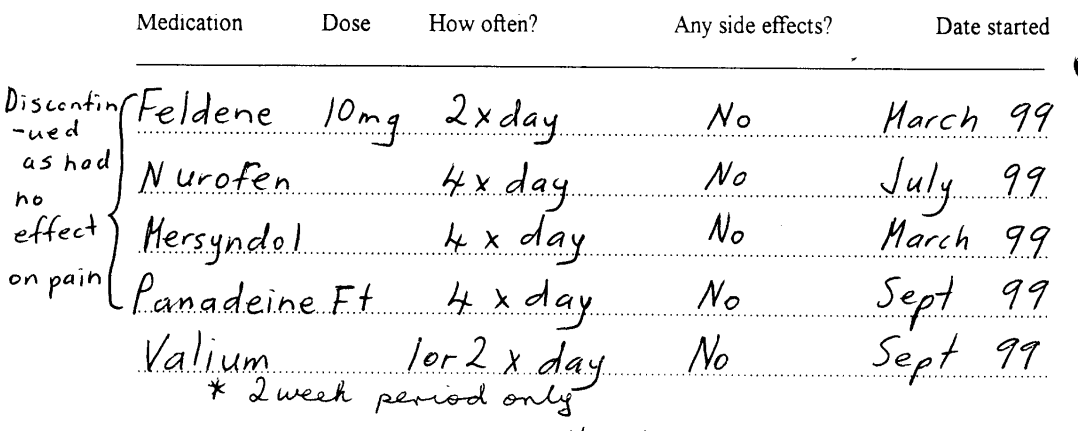
Treatment and Pain Management Guidelines

1. *Medication rationalisation*

The selection of appropriate drugs for the treatment of neuropathic pain must take into account a number of principles: (i) adequate dose to achieve a therapeutic effect, (ii) titration of dose to minimise side effects, (iii) consideration of background medical

conditions that may influence the pharmacokinetic profile of the drug, and (iv) drug interactions. Drugs appropriate for acute pain management may be, and often are, contraindicated for chronic pain management. Polypharmacy may reduce the overall amount of drug needed, but the dose must be calculated for each drug given. Blood concentrations of drugs may need to be monitored to assess whether therapeutic concentrations are being reached. In medication rationalisation, the implementation of therapeutic drugs is crucial to effective pain management, yet an equally important task is to make recommendations for discontinuing other current, but inappropriate drugs, that are often used by patients with chronic pain. In particular, for neuropathic pain, the discontinuation of benzodiazepines and opioid drugs is crucial due to issues of central sensitisation, tolerance and poor response (Figure 8). Management of neuropathic orofacial pain usually entails introducing the oral systemic first-line classes of drugs of the tricyclic antidepressants and / or the anticonvulsants.

Figure 8. Inappropriate use of drugs for treating neuropathic pain. A single, 46-year-old female with neuropathic oral pain of one year duration presented with the following drug history. Opioid and nonsteroidal antiinflammatory drugs were trialed by general practitioners but were ineffective, a feature with neuropathic pain. She had undergone repetitive endodontic therapy (three times) to 'cure' the pain and she was "never free from pain". A six week trial of topical capsaicin instigated by the Pain Management and Research Centre reduced the pain from 5/10 to 3/10 as measured on the numerical rating scale, and she reported the occasional pain free day. Psychological assessment indicated background levels of stress and following psychological interventional strategies she has reported "no pain at all".



Tricyclic antidepressants

Tricyclic antidepressants (TCAs) have a valuable role in the management of chronic pain, and the institution of a low dose of a TCA such as amitriptyline or nortriptyline as a first-line drug is frequently employed. Amitriptyline has both catecholaminergic and serotonergic activities. The dose is slowly increased from 25 mg *nocte* for the first week, to 50 mg *nocte* for the second week, and then to 75 mg *nocte* for the third and ensuing weeks, to build up patient tolerance to side effects such as sedation. For the elderly, it is prudent to commence with a dose of 10 mg *nocte* for the first week. It is necessary to maintain the tricyclic for at least 12-18 months before considering the discontinuation of the drug (78). TCAs provide background analgesia by preventing the reuptake of serotonin (and / or noradrenaline) at central sites. Serotonin and noradrenaline have analgetic or algogenic properties that are site specific; increased concentrations of serotonin and noradrenaline at central receptor sites provide analgesia, while increased concentrations at peripheral sites cause pain. Common side effects of TCAs include anticholinergic effects such as xerostomia, weight gain, and sedation. More serious side effects include postural hypotension and arrhythmia, and there is an overdose mortality rate of 11-15 times compared with anticonvulsants. The frequent side effect of sedation, however, may be beneficial as it assists the patient's sleep pattern, which is often disturbed in chronic pain patients. TCAs are more acceptable for anxiolysis and night sedation than diazepam. The newer tetracyclic antidepressants are less toxic and have fewer side effects than the tricyclics, but do not appear to possess the analgetic properties of tricyclics.

Anticonvulsant drugs

Anticonvulsant drugs are appropriate where the pain has sharp, shooting, paroxysmal qualities. They have a membrane stabilising effect, causing a general reduction in the excitability of neurons. Anticonvulsants to be considered include carbamazepine and sodium valproate. Carbamazepine can increase brain concentrations of serotonin and sodium valproate can increase concentrations of gamma-aminobutyric acid (GABA). The starting dose for carbamazepine is usually 100 mg *tds* (and 100 mg *nocte* for elderly patients) and is gradually increased until a therapeutic effect is achieved (or side effects occur). The effective dose may need to be as high as 400 mg *tds*, but at this dose side effects of sedation, ataxia and gastrointestinal upset are common. Regular blood counts are necessary due to the possibility of thrombocytopenia and bone marrow depression. Sodium valproate appears to be less toxic than carbamazepine, and is generally better tolerated. Gastrointestinal disturbance and sedation are common side effects. In addition, disturbances of hepatic function may occur with sodium valproate and routine measurement of liver enzymes is necessary. Phenytoin is a second- or third-line anticonvulsant as it has a narrow therapeutic range and a potential side effect is marked gingival hyperplasia. Gabapentin is a recently introduced anticonvulsant that has an improved therapeutic effect to side effect ratio. However, its relatively high cost (~ $250 per monthly script) currently restricts its more widespread use as the drug is not currently listed with the Australian Pharmaceutical Benefit Scheme for pain management, in spite of published reports establishing its efficacy for managing neuropathic pain (79, 80, 81).

Other oral systemic antineuropathic drugs

Clonazepam is a benzodiazepine primarily used for treating epilepsy, and accordingly its anticonvulsant properties render it useful for sharp, lancinating pain. Mexiletine, a cardiac antiarrhythmic agent and lignocaine analogue, is useful and should be considered if the patient has had a positive response to a lignocaine infusion. Drugs including long acting opioids, that contain morphine as the active agent, should be used with caution and as a last resort. There is the possibility that over a period of time (after 2 years) opioids may increase the pain (seen as a resistance or tolerance) through central sensitisation, by an increase in central concentrations of protein kinase C (26). Patients with a history of chemical dependency should be excluded and there should be one prescriber and one dispenser. Short acting opioid analgetics, such as codeine and pethidine, often used for acute pain, are contraindicated in the long term management of neuropathic orofacial pain. NSAIDS, such as ibuprofen, have been shown to be effective for diabetic neuropathy but adverse effects, including gastrointestinal ulceration, preclude their long term use. Several other drugs and routes of administration, for example, intravenous ketamine and topical aspirin, are effective for neuropathic pain, but may be limited in their application for intraoral use due to side effects (e.g. the 'aspirin burn' when aspirin is left to dissolve in the buccal sulcus). A systematic review of drug trials for peripheral neuropathic pain has been recently published (82).

Topical agents

Capsaicin (8-methyl-N-vanillyl-6-noneamide, cayenne pepper) is derived from capsicum fruit and its prime role for medical applications has been for the treatment of dermal lesions of postherpetic neuralgia (83). The substance has both algesic and analgetic properties, and depending on the concentration used, capsaicin can selectively activate, deactivate and even destroy small diameter afferents, but leaves larger diameter afferents and the CNS intact. It can deplete several algogenic peptides, including substance P, calcitonin gene-related peptide, somatostatin and vasoactive intestinal peptide. Capsaicin is a topical, first-line antineuropathic agent with established efficacy in treating neuropathic oral pain. One report assessed the topical application of capsaicin to 30 patients with neuropathic orofacial pain (8). In this study patients were instructed to apply the agent (0.025% capsaicin) for three minutes, twice daily, to the area of intraoral pain. To limit any stinging / burning sensation from applying capsaicin, patients prerinsed their mouths with a topical anaesthetic mouthwash for three minutes. Results of the capsaicin trial showed a significant pain reduction in the test group. Nineteen patients reported a significant reduction in pain that ranged from 10-100% (mean = 58±25 SD). At long term review (mean = 13 months), there was no significant change in pain compared with results from the four week capsaicin trial; the positive responders had maintained a mean pain reduction of 50% (±34 SD). Other topical preparations specific for dermal use in conditions such as postherpetic neuralgia include powdered aspirin in chloroform or ethyl ether, and indomethacin, which inhibits prostaglandin synthesis (84).

2. *Sympathetic blockade*

There is limited information on the management of the SMP component of neuropathic orofacial pain. The recommended technique is a series of stellate blocks conducted by an anaesthetist. The concept is to repetitively break the pain cycle administering one block per week for four to six consecutive weeks using a long acting local anaesthetic such as bupivacaine. In an uncontrolled study involving five subjects, researchers administered repeat stellate blocks using variable protocols with all subjects reporting pain reduction at follow up (ten months – three years) (9). A possible alternative treatment is clonidine, an α_2-adrenoceptor agonist that reduces sympathetic activity in the brainstem. Peripherally, clonidine acts at prejunctional α_2-receptors to reduce noradrenaline release. Transdermal applications of clonidine reduce pain and hyperalgesia at the local site of application. An uncontrolled study assessed its efficacy for treating neuropathic orofacial pain. Clonidine was applied, 0.2 mg/g in a cream base, four times a day to the site of pain; results showed that 6/12 patients had a positive response but with a wide variability in reducing pain intensity, ranging from 10-90% (85).

3. Temporomandibular disorder

Approximately two thirds of patients with neuropathic orofacial pain subsequently develop a TMD (8). Treatment of TMD, without attending to the causal neuropathic pain factor, however, does little in reducing the overall pain problem. Pain arising from TMD is predominantly due to bruxism. This can result in myofascial pain from masticatory muscle spasm (jaw clenching) and sensitisation of C-fibres in the periodontal, periapical and pulpal tissues of the oral cavity. Accordingly, there is a range of options available to help manage

the condition including drugs, physiotherapy, and occlusal splints and other dental appliances. Drugs such as NSAIDS are appropriate for acute muscle spasm but should be used with caution; ideally NSAIDS should only be considered as a rescue medication in the chronic pain patient.

Physiotherapy encompasses a broad range of treatments that is initiated by the physiotherapist, and subsequently maintained by the patient. Initial treatment can include ultrasound, short wave diathermy, and laser to the affected musculature. Further professional instruction should be given to the patient regarding jaw (and neck) extension exercises and these should be rigorously pursued on a home basis by the patient. Other simple home physiotherapy measures include the frequent application of heat packs.

Specific dental treatment can use occlusal splints to break the muscle spasm and to prevent tooth attrition. It should be noted, however, that while there is extensive documentation on splint design and clinical usage, well designed controlled studies indicate a significant placebo response from splints (86). On the other hand, where there is clear evidence of occlusal problems as a result of the extraction of teeth carried out in an attempt to cure the pain, then an occlusal splint as a prelude to occlusal rehabilitation with a permanent prosthetic appliance is warranted.

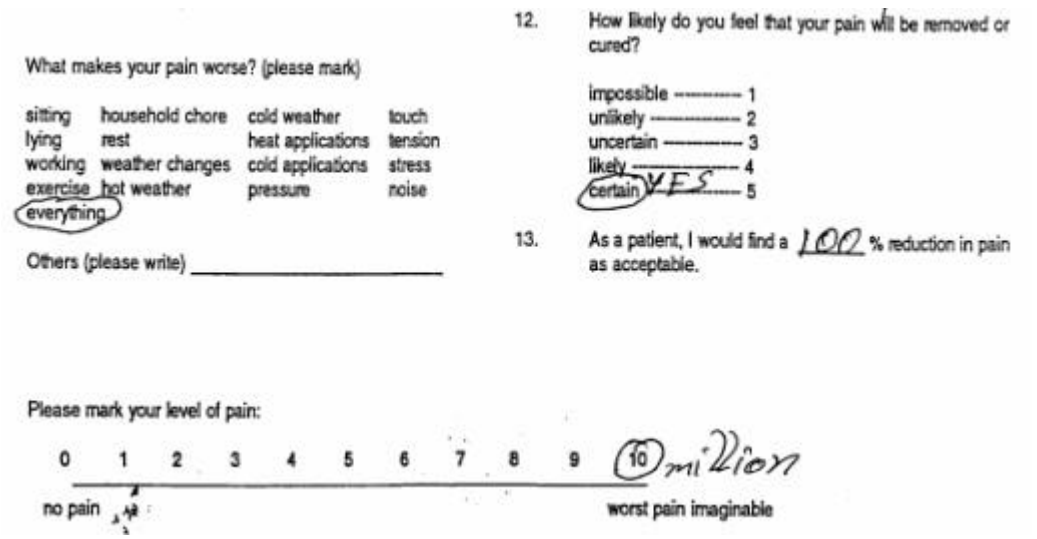
4. Psychological factors

The MPQ, in addition to providing information on sensory qualities of pain and subsequent appropriate choices for drug trials, offers pertinent information on aspects of psychological distress. For example, patients with trigeminal neuralgia often list sensory descriptors such as shooting, stabbing and cutting that indicates trials of anticonvulsant drugs are indicated, yet they tend to be economical in the use of descriptive words. However, chronic pain patients with a nociceptive basis to their pain problem and significant psychological distress are likely to return a longer list of descriptors and include words such as sickening, terrifying and cruel as qualities of their pain. Specialist psychological or psychiatric assessment is a requisite for patients listing multiple, affective pain word descriptors (87).

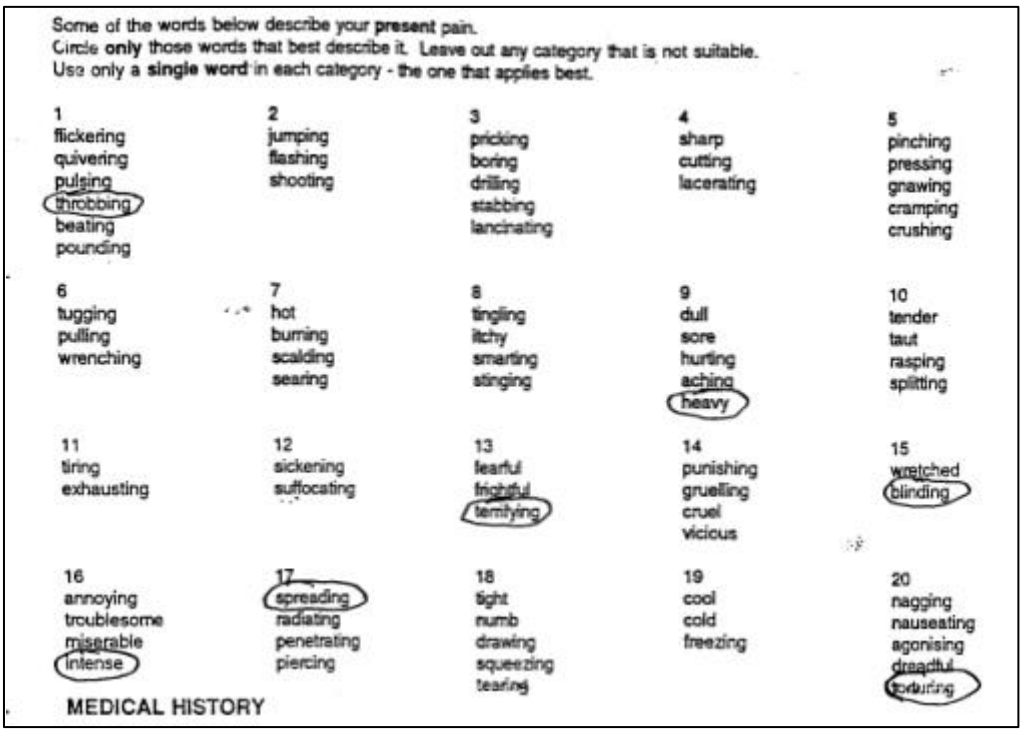
For any patient with a chronic pain condition, the potential role of psychological factors in magnifying, minimising, or maintaining pain should not be underestimated. The use of written information in the form of a pain questionnaire can offer valuable information on the magnification of pain and unrealistic expectations of treatments (Figure 9). One study demonstrated that the amount of treatment that patients with back pain received bore more relationship to the distress and illness behaviour they exhibited, than to the physical disease (88). It is imperative that any chronic pain patient undergoes assessment by a clinical psychologist and / or psychiatrist with expertise in pain medicine. Pain is a subjective experience and is determined by psychological and environmental factors, in addition to the underlying pathology. There can be wide individual variation of

Figure 9. Psychological variables in chronic pain. A 38-year-old female with neuropathic pain of two years duration, magnifying her pain report and having unrealistic expectations of treatment. (a) There was a pain score of "10 million", yet she was "certain" that the pain would be cured, and only a "100% reduction in pain was acceptable". (b) There was a history of past physical abuse including torture in her country of birth and she described her pain as having "terrifying" and "torturing" qualities on the McGill Pain Questionnaire.

(a)



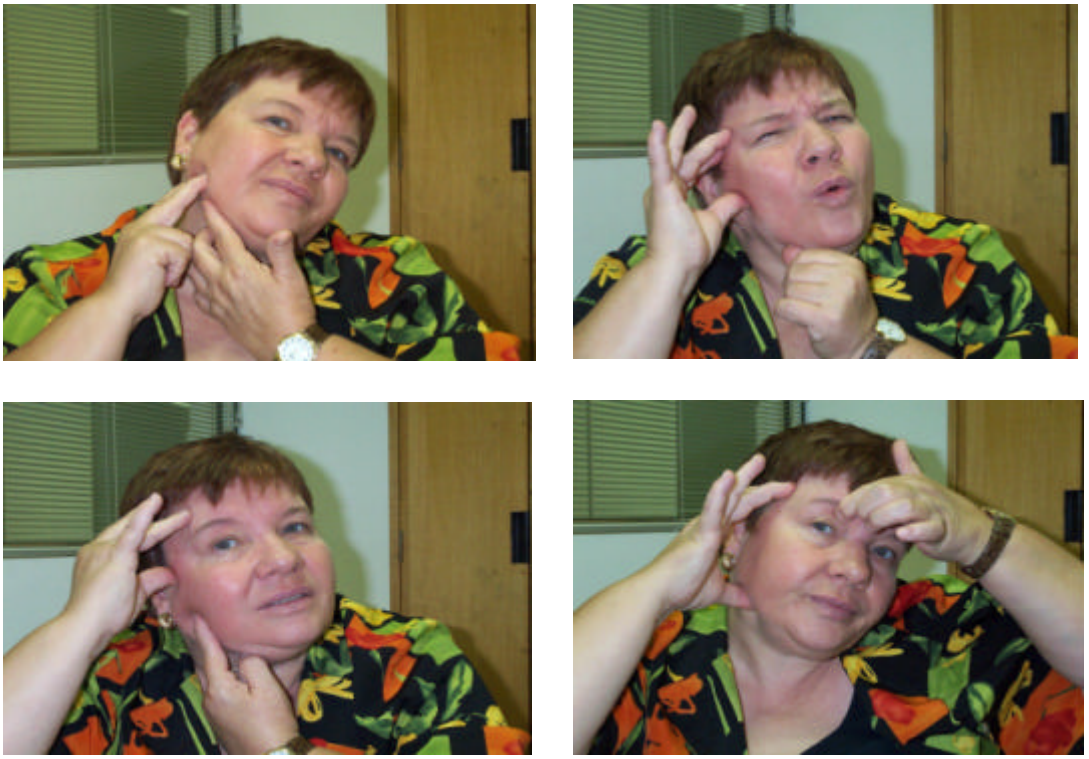
(b)



how a patient demonstrates his / her pain to their practitioner(s) (Figure 10). Pain may often lead to anxiety and tension that, in turn, may increase the pain. Furthermore, pain intensity ratings are doubled when stress is present (89), and other studies have previously shown a strong and positive correlation between pain severity and impairment of activities (90, 91).

The chronic pain patient may be unable to cope with his / her situation, which can lead to loss of self confidence, avoidance of others, and feelings of hopelessness and helplessness. They may blame the clinician for failing to solve the problem and there can be outright hostility and anger, and perhaps litigation, directed towards practitioners who they perceive have made the condition worse through inappropriate treatment. This can lead to an inability to communicate effectively and constructively with practitioners. The clinical psychologist (and psychiatrist to identify organic disorders) serves a key role to enable the patient to reach a better understanding of important pain management issues such as achieving a realistic outcome, self responsibility for long term management, and acceptance of the clinician's advice. Operant conditioning may exist between patient and doctor, for example the continual advice on pain relief or cure for intractable chronic pain, and secondary emotional gain may be present between patient and caregiver, with the continuance of pain to obtain support, sympathy and control (22).

Figure 10. Expression of facial pain and psychological distress. A 55-year-old female with neuropathic orofacial pain and secondary temporomandibualr disorder displaying her pain. She had suffered a facial assault by a close female relative over a family dispute. She was in great distress and there were significant psychological factors involved.



It is important to obtain positive evidence of psychological factors playing a causal role as well; diagnosis by exclusion is clearly to be avoided. If a patient appears to have no clear pathological basis to his / her pain, referral for psychological assessment must be handled carefully lest the patient perceives it as being told "the pain is in your head", which is likely to result in rejection of advice. If psychological assessment is sought, it should only be performed by a psychiatrist or clinical psychologist who has expertise in the field of pain, and the reason for the referral should be fully explained to the patient. For example, it should be explained that such pain problems are complex, and are associated with suffering and distress. In order to get a complete understanding of this pain, it is thus highly advisable to have input from appropriately experienced clinicians to assess the psychological aspects of pain, and the problems it causes. Most importantly, the medical / dental practitioner and the patient must have a common understanding prior to psychological / psychiatric assessments that the patient "is not crazy" or "imagining the pain". For the referring clinician, it should be noted it is possible that previously undetected pathophysiology may exist in conditions that can be difficult to diagnose such as neuropathic orofacial pain. Psychological strategies employed in pain management include cognitive behavioural therapy (modifying attitudes, beliefs and expectations), relaxation and biofeedback, and hypnosis.

In summary, pain management programmes are recommended for those who are not coping with their pain with the aims to (i) increase self perceived control over pain, (ii) increase self perceived independence, (iii) increase levels of physical and social activity,

and (iv) reduce levels of emotional distress. On a pharmacological basis there is the need to rationalise (discontinue or reduce) the use of inappropriate medication.

CHAPTER 5

Case Studies

Case Study 1

History, presentation and investigations

A 43-year-old female, married with three children, described a ten year pain history. She lived with her family, worked as a travel consultant, and was a social drinker (1 alcoholic drink per day). She claimed there was constant pain in tooth 16 (maxillary right first molar - International Dental Notation Classification) in the period from 1988-91. The tooth was sensitive to pressure, and hot and cold stimuli. Her general dental practitioner treated the tooth with root canal therapy (RCT) in 1991, and a crown was subsequently placed. The pain persisted and there was an increase in sensitivity to percussion and cold stimuli. The dentist carried out a further RCT but there was no change in her symptomatology. She was then referred to an endodontist. The endodontist was unable to negotiate intracanal ledges and thus periapical surgery was performed in December, 1997. Healing was uneventful, however the pain continued. The adjacent tooth (15) then became sensitive to cold stimuli. An endodontic colleague who believed that the area of pain (15-16) was not associated with 16 sought a further opinion. An opinion from a prosthodontist followed and an occlusal splint was issued. The splint therapy was only “partially beneficial” (patient’s words) and she discontinued wearing the appliance. Periapical surgery was again performed on 16 in June, 1998. No pathology was detected at the time of surgery, healing

was again uneventful, but the pain persisted. In August, 1998, 15 was still sensitive to cold stimuli, the pulp was extirpated and a coticosteroid / antibiotic paste (Ledermix, Lederle Laboratories, Wolfrathausen, Germany) placed. There was still no change in symptomatology and the patient was referred by the endodontist to the PMRC for multidisciplinary pain assessment.

Other investigations performed during the course of endodontic treatment included CT scan (no pathology detected), general medical assessments and an opinion from an ear, nose and throat surgeon. The patient's previous dental history included the removal of supernumerary teeth at seven years of age, and the surgical removal of impacted third molar teeth and other supernumerary teeth at 14 years of age. Her medical history was unremarkable apart from an allergy to penicillin based drugs.

Pain characteristics and psychological factors

The pain was situated in the region of the 16 tooth and the adjacent buccal gingivae and mucosa. The pain had also spread extraorally to affect the facial tissues around the right temporomandibular joint. The temporal quality of pain as reported by the patient was constant, but there were occasional short periods without pain. Pain intensity as measured by the numerical rating scale showed the pain to have a usual level of 5/10, that varied from 0-9 during the day, often no pain on awakening, but 7-9/10 by the afternoon (0 = no pain, 10 = worst pain imaginable). On the verbal descriptor scale, the pain was medium to severe. Modalities that worsened the pain included local pressure on the gingivae, tension,

tiredness, eating, and dental procedures. Modalities that ameliorated the pain included sleep, analgetics and "keeping my mind off the pain". MPQ word descriptors listed by the patient included pounding, flashing, gnawing, hot, aching and tender sensory qualities, and exhausting, troublesome, penetrating and nagging affective / miscellaneous qualities. Clinical examination showed a TMD was present and had developed subsequent to the neuropathic oral pain. The TMD signs and symptoms included temporomandibular joint pain, headaches, blocked ear, bruxism, sinusitis-like symptoms, occasional facial numbness, and episodes of swelling and heat in the face and in the buccal vestibule of the lip.

There was no obvious clinical depression as determined by psychological assessment and completion of several psychological questionnaires including the MOS Health Survey (92), the Beck Depression Inventory (93), and the Pain Self-Efficacy Questionnaire (94). The patient had indicated at her first pain centre consultation that even with medical treatment, she realistically expected the pain "will not change". Despite her lack of confidence in the prognosis of the condition, she was interested to find out what was the diagnosis of the condition and the cause of her pain.

Diagnosis and management

The medication at the time of her referral included prescription and 'over the counter' drugs: two Panadol tabs (paracetamol 500 mg tabs) *prn*, two Nurofen tabs (ibuprofen 200 mg tabs) *prn*, and Rohypnol ½ tab (flunitrazepam 2 mg tabs) *prn*. The patient was

diagnosed with neuropathic orofacial pain with a secondary TMD. A six week trial of Zostrix (0.025% capsaicin) applied topically to the site of intraoral pain was commenced, concurrent with the introduction of a TCA. The TCA was amitriptyline; this was increased from 25 mg *nocte* to 75 mg *nocte* over three weeks and then maintained at that dosage. At a review at two months following the combined treatment, the patient claimed a 90% reduction in pain. She currently uses the capsaicin on an occasional basis when there is breakthrough pain. This reduces the pain back to basal levels in two to three days. Her medical doctor, who currently manages the patient (amitriptyline prescriptions), reported slightly raised liver enzymes (a rare side effect of amitriptyline) that is being monitored.

Case Study 2

History, presentation and investigations

A 23-year-old healthy male, a final year medical student, described a four year history of chronic pain situated in the left jaw and face. The original cause of the pain was thought to be chronic infection of the 38 (mandibular left third molar). An oral surgeon extracted the tooth but pain and infection persisted and another dentist extracted the adjacent second molar several months later. There were no further episodes of infection but the pain was still present and then spread to the maxillary left molars.

There had been no diagnosis that could explain the chronic pain complaint from the investigations carried out over the four year history. During the course of the pain, he had seen three oral surgeons and one dentist who conducted clinical examinations, and

periapical and orthopantomogram (OPG) radiographs. Two ear, nose and throat surgeons, two neurologists, an allergy specialist and four general medical practitioners also investigated him. In addition to routine clinical assessments by the medical specialists, investigations included blood tests, and CT and MRI scans of the brain.

Pain characteristics and psychological factors

The pain was centred in the left mandible 70% of the time, and 30% of the time it was centred in the left maxilla. The pain intensity varied from 1-5/10 with severe pain episodes rated 8/10. There were periods of being pain free and of severe pain, both periods lasting days or weeks. Pain qualities ticked on the MPQ were: throbbing, sharp, tugging, tingling, aching, taut, tiring, punishing, intense, spreading, tight, cold and dreadful.

Psychologically, the patient believed that underlying, "perhaps sinister" pathology was initially responsible for the pain. Later, unremarkable findings from investigations then led him to conclude it was not life-threatening pathology but the pain had a "marked effect". He felt "frustrated, despondent and anger towards unsympathetic doctors, no suicidal thoughts but periods of mild depression". He questioned himself "can your mind create this pain from psychological and social factors?; I am doubtful of my normal senses - am I hallucinating regarding this pain?" He intentionally hid his condition from medical colleagues as he believed there was a stigma associated with chronic pain - a belief he attributed to the attitudes of his medical teachers (consultants and registrars) that these patients were "constantly complaining, narcotic dependent, and had personalities that were warped by

the pain problem". Study and university results were affected and he believed this would result in restricted employment opportunities. He relied on his parents for ongoing support and his social life was greatly affected with an 80% decline in pursuing hobbies and social activities.

Diagnosis and management

The patient self referred himself to a specialist oral surgical practice in a regional city visited on a part time basis by the author. He had previously self prescribed Tofranil (imipramine 10 mg tabs) and discontinued it after 1-2 days due to side effects ("it was awful and I felt like a zombie even on 10 mg"). The patient was diagnosed with neuropathic orofacial pain with a secondary TMD but he declined referral for multidisciplinary pain assessment at the author's institution. There was marked spasm in the left masseter muscle. He undertook a six week trial of Zostrix (0.025% capsaicin) but it was not beneficial. The patient currently self medicates and uses rescue doses once / twice a month of Imigram (sumatriptan 50 mg tabs) and 4-6 tabs of Panadeine Forte (paracetamol 500 mg, codeine 30 mg per tab); his current use of medication for chronic pain is not recommended. In addition, he uses distraction strategies (work, study, television) and relaxation techniques to manage the pain.

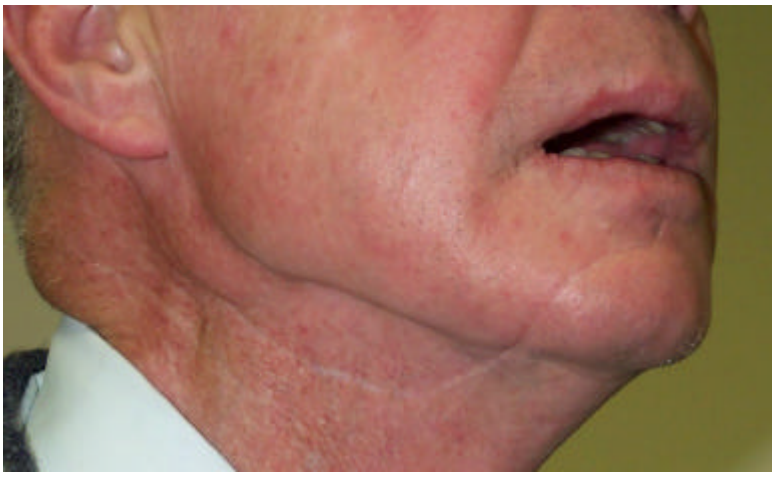
Case study 3

A 55-year-old Caucasian male underwent cancer surgery for carcinoma of the soft palate in 1995. He had a background medical condition of Charcot-Marie-Tooth disease. For the surgery, he had his mandible split for access. Three months after the surgery he complained of pain at the intraoral site of the incision passing over the mandibular alveolar crest (Figure 11). He described the pain as "very painful" and scored 6/10 on the NRS. MPQ word descriptors ascribed to the pain included crushing, pulling, tiring, annoying, radiating and numb qualities. At the time of his first pain management consultation he reported poor pain relief using a preparation containing 30 mg codeine and 300 mg paracetamol per tablet, with an intake of 8 tablets per day for 3 years. He had previously tried mexiletine (200 mg), amitriptyline (50 mg), and carbamazepine (200 mg) daily for pain relief but had discontinued these medications, as they were ineffective. He was engaged in full time employment, and was in a stable, happy marriage with two children. His responses to psychological questionnaires revealed he had a positive attitude towards managing chronic pain. However, based on his previous three years of failed medical treatments he believed that his pain condition would get worse.

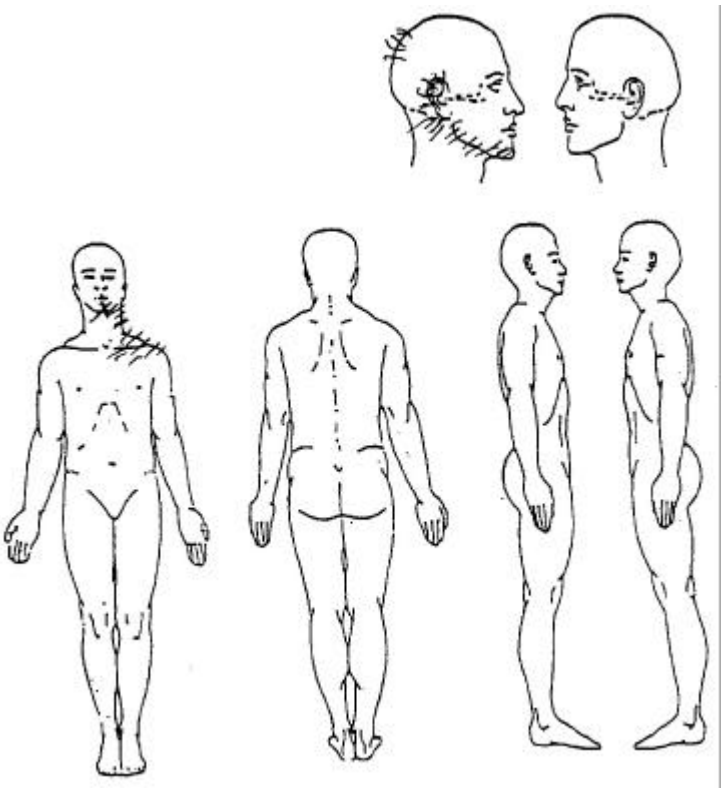
The patient underwent a trial of topical capsaicin that was applied to the site of the incision. For the trial he applied a topical anaesthetic mouthrinse to the mucosa for three minutes then followed by a three minute application of 0.025% capsaicin cream (Zostrix). This was carried out morning and evening for six weeks. At his review

Figure 11. Case study 3: (a) photograph of facial profile and external scars four years after cancer resection, (b) the painful site was the incision line over the mandibular alveolar crest (indicated by **X**) and radiating along the mandible and into the right side of the neck (N.B. patient error on shading left side of neck).

(a)



(b)



appointment at eight weeks he reported “very good pain relief” and had ceased his codeine / paracetamol intake entirely.

Several features of this case are worthy of comment. The head and neck surgeon who had carried out the operation was pleased with the surgical result and the patient was being reviewed every six months for possible recurrence. The surgeon initially thought that the pain may have been due to recurrence but there were no other features suggestive of recurrence and he was unable to explain to the patient the nature or source of his pain. The surgeon declined responsibility for managing the persistent pain and referred him to his local doctor for pain relief. His doctor had considered the pain to be neuropathic in origin and conducted trials of mexiletine, amitriptyline, and carbamazepine. However, while the drug selections were appropriate for this patient, the dosage of all three drugs was in the subtherapeutic range. It is likely that the patient would have gained benefit at dosages of mexiletine 600 mg (200 mg *tds*), amitriptyline 75 mg (*nocte*), and carbamazepine 600 mg (200 mg *tds*). The long term use of codeine was ill-advised and he continued its use for three years despite the drug providing only marginal benefit. It is likely that had the surgeon been knowledgable about neuropathic pain, the early intervention of capsaicin would have prevented three years of unnecessary pain and suffering.

Psychological assessment

The patient was well motivated, as he did not want the pain to disrupt his marriage or work. He had realistic expectations of treatment - a 50% reduction in pain as being

acceptable to live with. He was satisfied with obtaining good pain relief and was not seeking complete pain relief. The patient had not demanded additional medication for further pain relief as he recognised that an increased drug dose may initiate drug side effects, thus potentially hampering his work performance and enjoyment of family life. By having a positive, hopeful attitude and agreeing to take the responsibility for his own improvement, he has complied with treatment guidelines, applying the capsaicin that is currently used sparingly. He continues to report excellent long term pain relief.

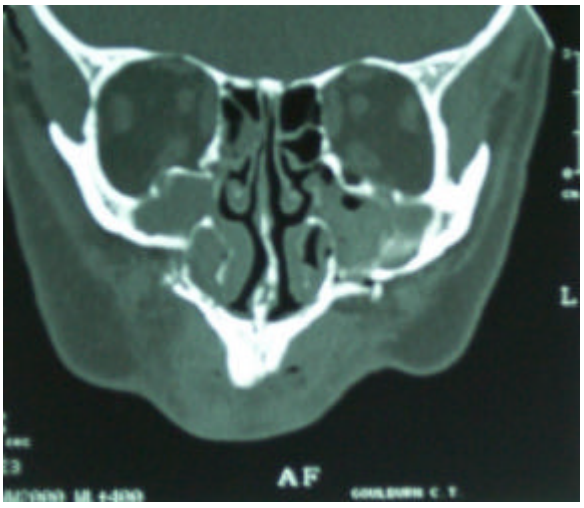
Case study 4

A 65-year-old Caucasian male, who in June, 1997 worked as a truck repairer, suffered severe maxillofacial trauma as a result of a crush injury at work. He incurred a Le Fort II fracture of the maxilla with significant displacement of the walls of the antrum and orbital floor (Figure 12). He subsequently underwent internal fixation with plates. He was referred to the PMRC for multidisciplinary assessments. The pain was constant and rated 6/10 on the NRS. MPQ word descriptors ascribed to the pain included throbbing, shooting, stabbing, sharp, aching and splitting sensory qualities, and exhausting, punishing, annoying, intense, piercing, tearing and torturing affective and evaluative qualities. He was married and lived with his wife. At the time of his referral he was taking 2 g paracetamol daily. He had previously trialed carbamazepine but it was discontinued after only two weeks due to excessive drowsiness. He reported a poor sleep pattern of only two hours sleep each night.

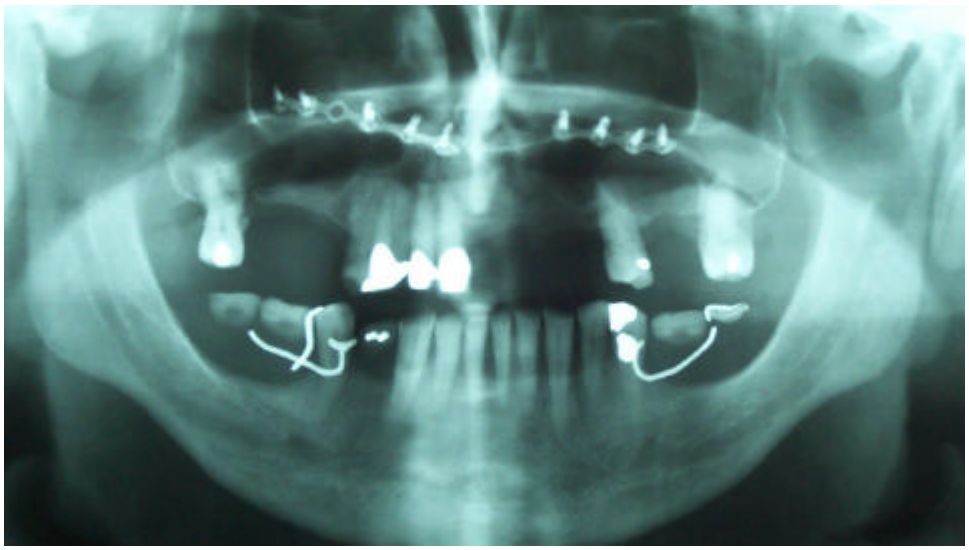
Figure 12. Case study 4: (a) facial photograph of patient two years after crush injury to the right side of the face, (b) CT section of facial fractures, (c) orthopantomogram of maxilla following open reduction and internal fixation of fractures, (d) pain map of multiple sites of pain showing neuropathic pain in the right maxilla and preexisting cervicogenic pain.

(a)

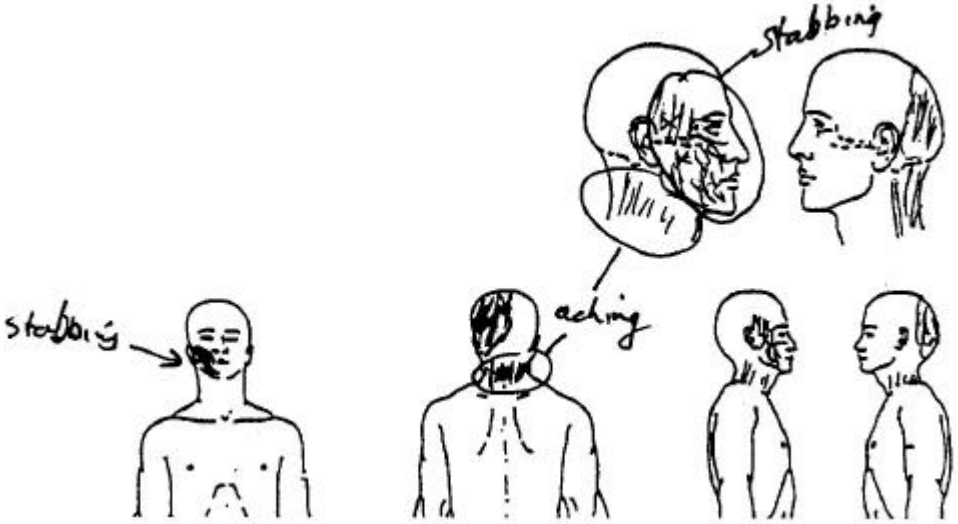
(b)



(c)



(d)



The patient was trialed on gabapentin with an escalating dose up to 900 mg daily over one week. At his review appointment at two months he had achieved a 50% reduction in the neuropathic facial pain by maintaining this regimen. He reported a slight occasional itch as the only side effect. He was still complaining of aching pain in the occipital region that was attributed to coexisting C 4/5 degenerative changes involving the facet joints (Figure 12(d)).

Psychological assessment

The patient was a self-made man. He had worked very hard over many years and had always been a hard-driving, rather perfectionistic, person. At the time of his injury, he owned and managed his business and was financially very comfortable. The injury, hospitalisation and continuing pain problem interfered with his business. Yet he could not bring himself to employ a manager whom he could trust to oversee the business. As a result, work-related stress continued to interact with pain to produce an angry and depressed man.

The patient sought 100% remission of facial and neck pain. He wanted his pre-injury face to be returned to him and would not be satisfied with anything less. He resisted the notion that this was an unrealistic expectation. As a result, despite his reports of a 50% pain reduction on gabapentin suggesting an excellent early result, the patient remained disappointed and distress levels remained high.

The results of the early gabapentin trial give rise to optimism that the neuropathic pain problem can be impacted by appropriate medication over a period of time. At the same time, psychological rigidity of attitude and expectations, high stress and sympathetic arousal, depression and an unwillingness to adapt to less favourable physical conditions threaten to undermine the pharmacological regimen.

CHAPTER 6

Future Directions in Neuropathic Pain Research: a Preliminary Study Evaluating an Application of High-Performance Liquid Chromatography-Mass Spectrometry

Introduction

As described previously in Chapter 3, there is a vast and diverse array of substances involved in the progression from acute to chronic pain. These substances involve protons and reactive oxygen species along with other recently identified substances such as excitatory amino acids, peptides, and hormones. A greater understanding of the various modulating effects of these native substances on each other could lead to the development of improved pharmacotherapeutic interventions aimed at preventing or restricting the development of a chronic pain state. Determination of any role(s) of the various peptides involved in mechanisms of causality of chronic pain involves a number of fundamental steps: (i) identification and confirmation of the substances involved, (ii) determination of concentrations of each substance, and (iii) identification of the biological effect(s) of each substance, and at what stage of the pain pathway (acute to chronic pain) the substance is involved. A barrier preventing a greater understanding of this complex process is the lack of availability of multiple specific assay techniques to measure the concentration of each analyte (amino acid / peptide) identified. Whereas immunoassay techniques have been employed in this role, usually affording measurement of the concentration of the substance in the femtomolar range, their disadvantages include a possible lack of specificity, lengthy

laboratory steps such as incubation times, and the determination of only one analyte per sample. This can subsequently limit the amount of information that can be potentially acquired from each sample, for example, research investigating multiple peptides and their active degradation products.

A technique that would allow the identification, confirmation and measurement of multiple analytes from a single prepared sample in a relatively short time would be of considerable benefit in extending the knowledge base of peptides involved in pain mechanisms. Moreover, a technique that could assay the various drugs used for treating neuropathic pain could secure further knowledge of their respective pharmacokinetic profiles leading to improved titration and dosage scheduling. One potentially useful technique for assaying drugs and biological substances of interest is high-performance liquid chromatography coupled to mass spectrometry (LC-MS).

This chapter describes a preliminary study evaluating LC-MS as a possible technique to overcome some of the limitations of immunoassay. The purpose of this study was to assess the utility of LC-MS by analysing mass spectra and retention times of several analytes of interest in a single sample. In this preliminary investigation the analytes used were drug and peptide standards. The peptides selected are documented to play a role in pain mechanisms, and drugs selected that are used in the diagnosis and management of neuropathic pain (lignocaine, capsaicin, carbamazepine, trimipramine) or nociceptive pain (morphine, fentanyl).

Reagents, drug and peptide standards

Formic acid (AJAX Laboratory Chemicals, Sydney, NSW, Australia) and acetonitrile (EM Science, Gibbstown, NJ, USA) were HPLC grade. The nebulising and desolvation gas for the mass spectrometer electrospray interface was nitrogen that was generated from a Pilot nitrogen generator (Carat P.L., Silverwater, NSW, Australia). Water was obtained from a Milli-Q water purification system (Millipore, Bedford, MA, USA). Solvents were filtered through 0.2 μm membrane filters (Millipore, Ireland) for use in liquid chromatography and electrospray analysis. Peptide standards were purchased from Auspep (Parkville, VIC, Australia) and Sigma-Aldrich (St. Louis, MO, USA). Drug standards were obtained from the hospital pharmacy (Royal North Shore Hospital, NSW, Australia). The substances tested are given in Table 2.

As the aim was to identify the retention times and *m/z* of the respective standards, and no subsequent biological samples were to be assayed, repeat injections of the mixture were not underaken to establish a validation curve at this stage of method development.

Instrumentation and chromatographic methods

For acquiring the mass spectra of the standards, separate direct injections into the mass spectrometer were made of each standard (10 μL of 5 μg/mL of each standard) using a 10 μL injection loop. The infusion flow rate was 10 μL/min provided by a Harvard

Apparatus syringe driver (Natick, MA, USA). Standards were dissolved in 50% acetonitrile, 0.5% formic acid for injection into the mass spectrometer.

High-performance liquid chromatography (HPLC) was carried out with a SMART System (Pharmacia Biotech) that was comprised of two 10 mL syringe pumps. Gradient chromatography was employed. Solvent A was 0.5% formic acid and solvent B was 90% acetonitrile, 0.5% formic acid; B increased 0% to 100% over 45 minutes. The flow rate was 200 µL/min and an 8:1 splitter was used for introduction of the effluent to the electrospray source. The HPLC column was a 5 µm particle size, 300Å pore size, 250 × 1 mm internal diameter, C8 Primesphere stainless steel column (Lot no. 136484) (Phenomenex, Torrance, CA, USA), with a 30 × 1 mm internal diameter Primesphere guard column (Lot no. 137100G) (Phenomenex, Torrance, CA, USA).

The mass spectrometer was a single quadrupole Micromass Platform II (Manchester, UK) equipped with an electrospray interface and was coupled to the HPLC or syringe driver. The acquisition parameters were as follows; ionisation mode ES+, capillary voltage 3.5 kV, HV lens 0.5 kV, skimmer offset 5 V, source temperature 120 °C, ion energy 10 V, LM resolution 15.0, HM resolution 15.0, multiplier 650 V. The flow rate of nitrogen for nebulisation was 10 L/h, and for desolvation was 300 L/h. Mass spectra were collected in continuum mode over a mass to charge (*m/z*) ratio range of 100 to 2000. Acquisition of data was performed with a scan every

eight seconds and an interscan interval of 0.1 seconds using MassLynx NT (Version 3.0) software or using the MaxEnt program within MassLynx.

Results

The 27 standards (Table 2) all showed characteristic mass spectra from separate direct infusions into the mass spectrometer e.g. Figure 13. All drugs showed the base peak (100% relative abundance) to have a *m/z* of $[M + 1H]^{1+}$. Some drugs displayed additional peaks representative of dimerisation and adduct formation (e.g. carbamazepine with *m/z* at 237 $[M + 1H]^{1+}$, dimerisation at 473 $[M + 2H]^{2+}$, Na^+ adducts at *m/z* 259 and 495) (Figure 13 (b)). The other 15 standards (11 peptides, prostaglandin E_2, serotonin, histamine, and the enzyme inhibitor antipain) varied with a *m/z* ranging from $[M + 1H]^{1+}$ to $[M + 4H]^{4+}$ (β-endorphin (1-27)) (Figure 13 (c)) with many peptides showing several *m/z* peaks.

On the LC-MS, all 27 analytes could be resolved by the mass spectrometer from a mixture injected into the LC-MS and standards eluted within the 45 minute LC-MS run time (Table 2, Figure 14). Analytes with similar *m/z* were resolved by chromatography as seen by different retention times (Figure 15). Several analytes had identical retention times (fentanyl, midazolam, kallidin and angiotensin II at 22.92 minutes; γ-endorphin and substance P at 26.62 minutes) that could be quantitated by their respective *m/z* (Figure 16).

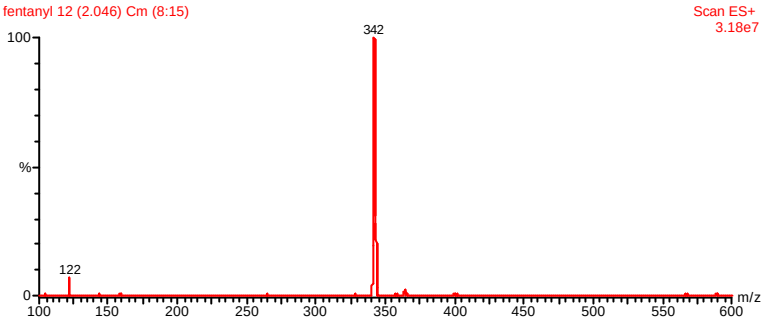
Table 2

Analyte *m/z* and retention time from direct MS infusions and LC-MS

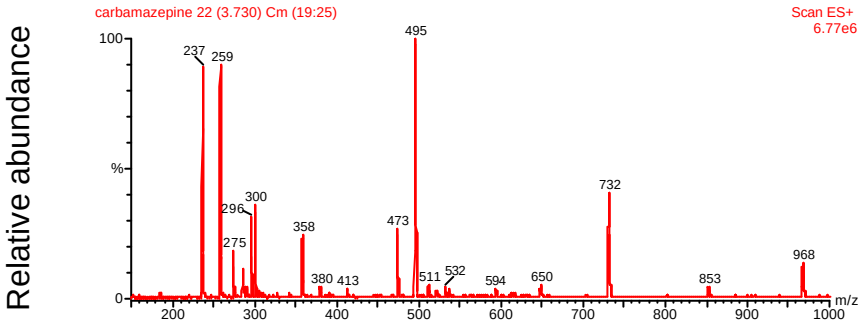
Analyte	**MW (Daltons)**	***m/z***	**Retention time (Minutes)**
Drug			
Prilocaine	220.3	221	5.41
Clonidine	230.1	230	6.59
Lignocaine	234.3	236	6.76
Carbamazepine	236.26	237	14.84
Mepivacaine	246.34	247	7.6
Ketoprofen	254.3	255	23.42
Diazepam	284.76	285	22.25
Morphine	285.33	289	36.72
Trimipramine	294.42	295	23.93
Capsaicin	305.4	306	26.29
Midazolam	325.77	326	22.92
Fentanyl	336.46	342	22.92
Peptide /other			
Histamine	111.2	112	4.23
Serotonin	176.2	177	4.23
Prostaglandin E_2	352.5	353	36.22
Antipain	604.7	303	22.41
Dermorphin	802.9	804	42.61
Angiotensin II	1046.2	524	22.92
Bradykinin	1060.2	531	33.86
Arg-vasopressin	1084.2	543	21.91
Neurokinin A	1133.3	567	23.26
Kallidin	1188.4	397	22.92
Substance P	1347.6	675	26.62
Somatostatin	1637.9	547	28.31
α-endorphin	1746.0	874	23.93
γ-endorphin	1859.1	930	26.62
β-endorphin (1-27)	3022.5	757	33.19

Figure 13. Mass spectral data of three standards (fentanyl, carbamazepine and β-endorphin (1-27)) from separate direct infusions (10 µL of 5 µg/mL of each standard dissolved in 50% acetonitrile, 0.5% formic acid) into the mass spectrometer: (a) fentanyl with *m/z* 342 $[M + 1H]^{1+}$, (b) carbamazepine with *m/z* 237 $[M + 1H]^{1+}$, dimerisation at 473 $[M + 2H]^{2+}$, and Na^{+} adducts at *m/z* 259 and 495, (c) β-endorphin (1-27) with multiple *m/z* at 757 $[M + 4H]^{4+}$ and 1009 $[M + 3H]^{3+}$ that was deconvoluted to identify MW at 3022.

(a)



(b)



(c)

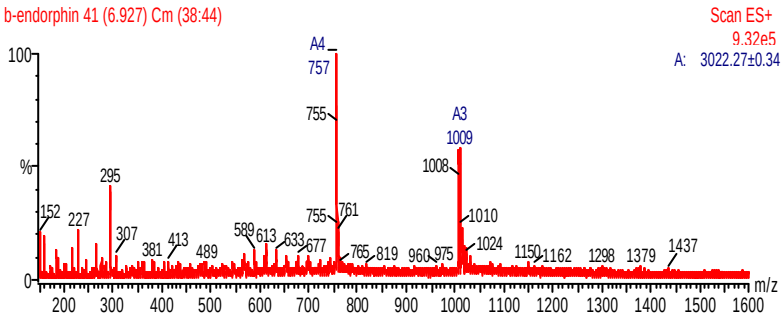


Figure 14. Mass spectrometer chromatogram from a single injection of a drug and peptide mix (10 µL of 5 µg/mL) into the LC-MS. Chromatographic conditions were: solvent A was 0.5% formic acid and solvent B was 90% acetonitrile, 0.5% formic acid; B increased 0% to 100% over 45 minutes; flow rate 200 µL/min and an 8:1 splitter to the electrospray source. Several large peaks displayed in the chromatogram (e.g. at 4.07 min and 42.78 min) are due to extraneous substances eluting from the chromatographic column as a result of the introduction of acetonitrile (organic mobile phase component) in the gradient for the peak at 4.07 min and high concentration of acetonitrile for the 42.78 min peak.

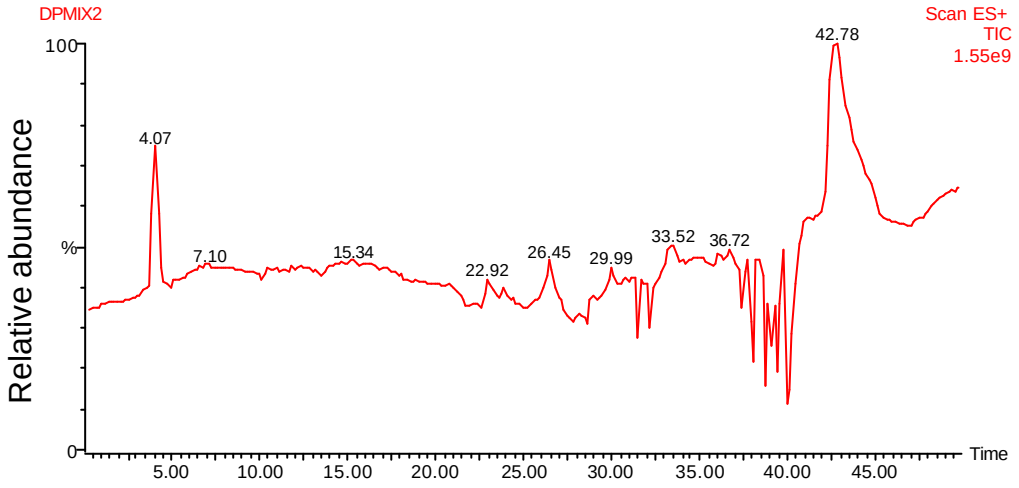


Figure 15. Separation of two standards with similar *m/z* by retention time: (a) capsaicin (MW 305.4, *m/z* 306 $[M + 1H]^{1+}$) showing a retention time of 26.29 minutes, (b) antipain (MW 604.7, *m/z* 303 $[M + 2H]^{2+}$) showing a retention time of 22.41 minutes.

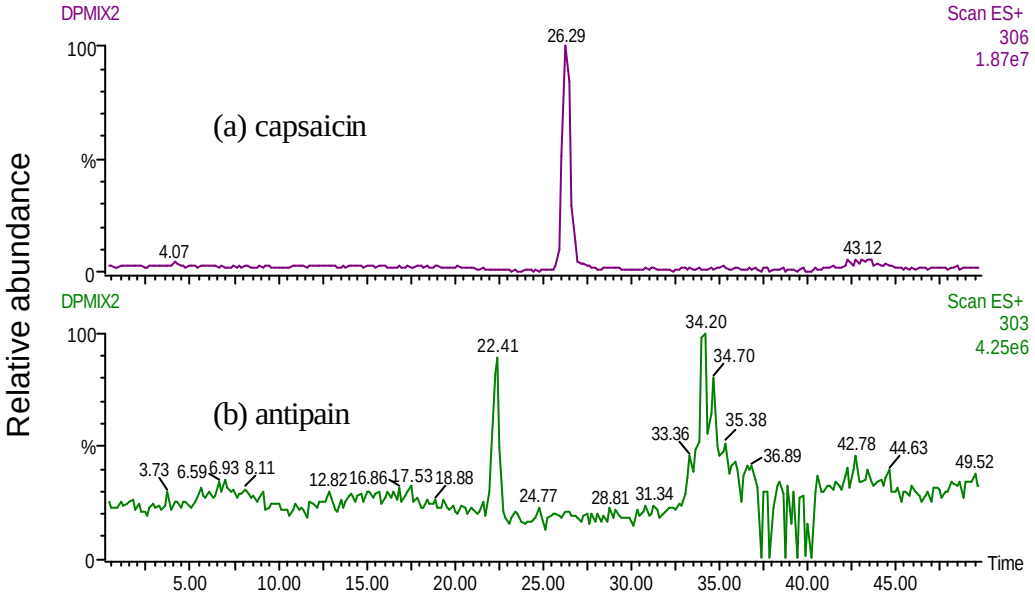
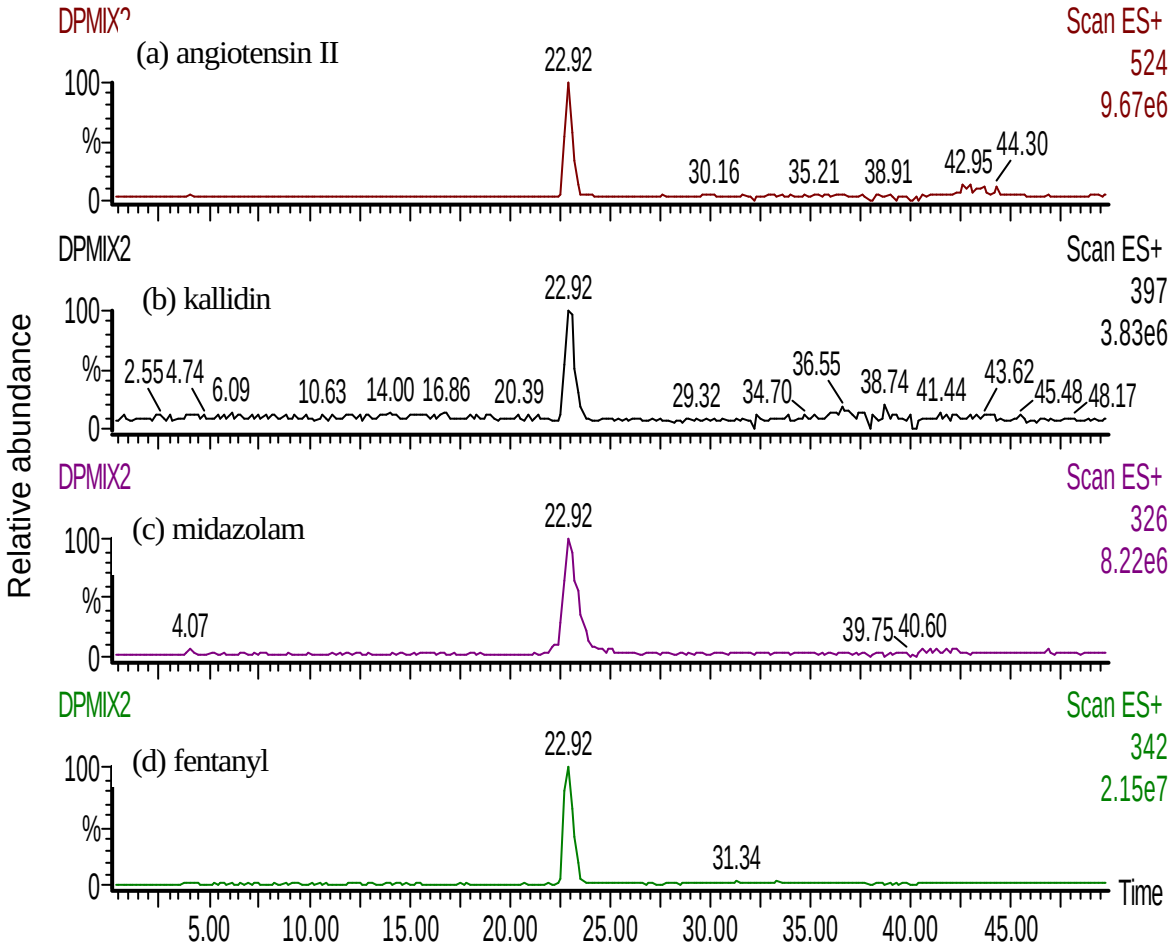


Figure 16. Confirmation of assignment and quantitation of four standards with identical retention times by different *m/z* (a) angiotensin II MW 1046.2, *m/z* 524 $[M + 2H]^{2+}$, (b) kallidin MW 1188.4, *m/z* 397 $[M + 2H]^{2+}$, (c) midazolam MW 325.77, *m/z* 326 $[M + 1H]^{1+}$, (d) fentanyl MW 336.46, *m/z* 342 $[M + 1H]^{1+}$.



Discussion

In this preliminary study, LC-MS showed itself to be a technique of tremendous utility by confirming the assignment of analyte identity to a broad range of drugs, endogenous substances, and one enzyme inhibitor. While gas chromatography-mass spectrometry (GC-MS) is a well proven instrument in drug analyses, the high temperatures needed in the GC makes it unsuitable for peptide analyses. Moreover, using a simple LC-MS method, such as described in this study, precludes the need for prior drug derivatisation, a necessity for some drugs employing GC-MS methodologies. The LC-MS was also useful in the separate confirmation of peptides with similar amino acid composition and sequence such as bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) and kallidin (Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg). This was accomplished by both the LC (separate retention times of bradykinin and kallidin, 33.86 and 22.92 minutes, respectively) and the MS (different *m/z* of 531 and 397, respectively). Where multiple analytes exhibited the same retention time, entering the *m/z* of the particular analyte of interest gave a value for its relative abundance that can be used to determine the concentration of the analyte from a validation curve. In this respect, the coupling of the MS to the LC overcomes a major problem with using LC by itself, as co-eluting substances confound peak identity and integration when LC is used as a single technique. In addition, LC-MS has an advantage over immunoassay techniques due to the necessity of separate immunoassays for each peptide.

In summary, from this preliminary study using standards, LC-MS appears to have superior utility for multiple drug and peptide analysis when compared to other techniques (GC-MS, immunoassay, HPLC). This should enable further knowledge to be gained concerning the biological processes involved in neuropathic pain, and the pharmacodynamic and pharmacokinetic profiles of drugs used in the management of pain.

CHAPTER 7

A Summary of this Treatise

The prevalence of neuropathic orofacial pain in society has yet to be accurately determined. The available reports are still limited to only a few retrospective studies. One report, nevertheless, stands out as being of great importance to the endodontic speciality group, with approximately 50% of patients in the study claiming pain as a result of endodontic treatment (9). However, it is impossible at this stage to state categorically that dental / endodontic treatment is a prime causal factor in the development of neuropathic pain. While various endodontic procedures employ mechanical and chemical trauma to pulpal and periodontal nociceptors, preexisting pulpitis may well be the trigger for neuropathic pain. For example, in the case of postherpetic neuralgia (shingles) of the skin, there is infection and inflammation without surgical intervention, yet the patient may develop a neuropathic pain. Formal, prospective epidemiological studies are warranted to establish the true prevalence of this condition associated with general dental treatment (restorations, scaling, extractions) and specifically, with endodontics.

Chronic pain involves nociception and / or neuropathy, pain, suffering and pain behaviour. The pathophysiology of neuropathic pain is complex and involves deafferentation, nerve sprouting, neuroma formation, sympathetic efferent activity and centralisation. A great deal of current research is attempting to further define the mechanisms involved in this pain state.

Our current knowledge is based on animal research models and on investigations of well-described human conditions such as postherpetic neuralgia and phantom limb pain. Published information on neuropathic pain states focus predominantly on anatomical locations arising from spinal cord dorsal root; there are scarce reports pertaining to the trigeminal sensory system. While the sensory nervous system displays identical physiological phenomena (nerve conduction) throughout the body, differences in the degree of sensory innervation, such as the highly innervated dental pulp and periodontal ligament, may play an important role in the acquisition of neuropathic orofacial pain.

Conceptually, chronic pain involves nociception and / or neuropathy, pain, suffering and pain behaviour. Early referral (within six months) of a patient with chronic pain to a multidisciplinary pain clinic is recommended, where possible, for comprehensive pain assessments by a medical pain specialist, clinical psychologist, physiotherapist and others (dentist, social worker, etc). Neuropathic orofacial pain is a condition that can be difficult to diagnose and treat. However, there are simple, yet effective, diagnostic procedures such as the MPQ and the utilisation of sequential analgetic blockade that can assist the clinician in reaching a diagnosis. Psychological factors are important to identify as they can profoundly influence pain and pain behaviour. For example, a patient may expect substantial or unequivocal pain relief despite many years of suffering and failed treatments. Moreover, inordinate pressures can be placed on clinicians by patients with chronic pain who seek to commandeer the direction of pain treatments by suggesting further ablation (extraction / further endodontic treatment), or inappropriate drug treatment regimens such

as opioid drugs to manage the pain. It is recognised that chronic orofacial pain conditions have similar pain intensity ratings, as indicated by the PRI(T) of the MPQ, compared with back pain, cancer pain and phantom limb pain (33). However, this important point is probably overlooked by the general public because chronic orofacial pain does not raise the emotive responses inherent in cancer pain, nor the government / business concerns of lost work productivity and related economic considerations associated with back pain.

Initial treatment and long term management must utilise a broad range of pharmacological and psychological measures individually tailored to the patient. The management of neuropathic pain arising from dental / maxillofacial injury, surgery and infection is similar to its management in other areas of the body.

The use of capsaicin can serve dual purposes, as both a diagnostic agent and as a therapeutic agent. Principles for drug utilisation include the rationalisation of drug regimens to reduce and eliminate, where possible, opioids, sedatives and other drugs of dependence, and initiation of long term low dose TCAs, and adjunct medications such as anticonvulsants (carbamazepine, sodium valproate) and membrane stabilisers (mexiletine). Ancillary physical interventions for patients with TMD secondary to neuropathic orofacial pain include physiotherapy to jaw, neck and other musculature, and occlusal splints where bruxism is causing tooth attrition.

Pain can be magnified or minimised by gender-related effects, socioeconomic variables, ethnocultural differences, pending litigation / compensation, secondary gain and drug abuse.

Thus, it is imperative that an assessment of the role of psychological and environmental factors be undertaken to subsequently instigate appropriate strategies. The practitioner should be aware of the following psychological variables in pain management: (i) unrealistic expectations, (ii) the motivation to improve, (iii) maintaining taught psychological coping skills and physical exercises, and (iv) accepting appropriate advice on the rationalisation of drugs. The institution of specialist psychological / psychiatric treatment should focus on the development of effective coping strategies (e.g. relaxation techniques, cognitive and behavioural strategies), problem solving skills, and dealing with unresolved issues in the patient's life. The clinician needs to acknowledge and understand that, as a consequence of long term pain and suffering, there may be dire effects on the family and on the patient's ability to have gainful employment.

It is both prudent for the clinician and beneficial to the patient that sufficient and relevant advice be given to the patient, especially a satisfactory understanding of the pathophysiology of neuropathic pain. The patient may have a history of many years of suffering and failed treatments, including unnecessary repetitive surgery. Unfortunately, in many cases of chronic neuropathic orofacial pain, both the general dental / medical practitioner and the specialist are bewildered by this pain state through their lack of knowledge. Utilisation of multidisciplinary pain assessments leads to a correct diagnosis and may well save many patients from having a great deal of further unnecessary treatment, expense and suffering. In addition, this would allow the subsequent implementation of

interventions individually tailored to improve the chances of obtaining a successful outcome for the afflicted individual.

A fundamental step to improve the management of patients with neuropathic pain lies in its early recognition by primary-care clinicians. Accordingly, the education of clinicians is an important area in the prevention and early treatment of patients with neuropathic pain. Formal training for professionals in multidisciplinary aspects of pain (neurobiology, pharmacology and psychology) is thus recommended. Applied knowledge should curtail the unfortunate, but frequent desire, for dental practitioners to carry out widespread pulp removal or the extraction of multiple teeth, in an attempt to 'cure the pain'.

Additionally, basic science researchers need to acquire a greater understanding of the complex biological processes involved in the pathophysiology of neuropathic pain. LC-MS is a powerful technique, and is potentially useful for identifying substances involved in these processes. Furthermore, from the described preliminary LC-MS study, the technique appears to have wide scope in measuring drugs of interest that are prescribed in the treatment of neuropathic pain. For future research, the next logical step is to evaluate its utility in the clinical setting by obtaining and assaying representative biological samples from patients with neuropathic pain. LC-MS would appear to offer the possibility of adding to the knowledge base on the neurobiology of pain, hence providing directions for the development of novel drugs. Furthermore, it is anticipated that the technique could identify and measure endogenous substances that may be released in psychological distress,

thereby suggesting a unique approach to quantifying distress and evaluating non-pharmacological approaches to pain treatments such as psychological interventions.

Bibliography

1. Merskey H, Bogduk N. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd ed. Seattle, IASP Press, 1994, pp. 53-6.

2. Rees RT, Harris M. Atypical odontalgia. Br J Oral Surg 1979; 16: 212-8.

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

4. Marbach JJ. Is phantom tooth pain a deafferentation (neuropathic) syndrome ? Part II: psychosocial considerations. Oral Surg Oral Med Oral Pathol 1993b; 75: 225-32.

5. Marbach JJ. Phantom tooth pain. J Endod 1978; 12: 362-72.

6. Brooke RI. Atypical odontalgia. Oral Surg Oral Med Oral Pathol 1980; 49: 196-9.

7. Pöllmann L. Determining factors of the phantom tooth. N Y State Dent J 1993; Dec: 42-5.

8. Vickers ER, Cousins MJ, Walker S, Chisholm K. Analysis of 50 patients with atypical odontalgia: a preliminary report on pharmacological procedures for diagnosis and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998a; 85: 24-32.

9. Lynch ME, Elgeneidy AK. The role of sympathetic activity in neuropathic orofacial pain. J Orofac Pain 1996; 10: 297-305.

10. Vickers ER, Harris RD. Neuropathic pain as a complication of maxillofacial injury and surgery. Middle East J Oral Maxillofac Surg (in press).

11. Turk DC, Meichenbaum D, Genest M. Pain and Behavioral Medicine. A Cognitive-behavioral Perspective. New York, Guilford Press, 1983.

12. Gamsa A. The role of psychological factors in chronic pain. I A half century of study. Pain 1994; 57: 5-155.

13. Vlaeyen WS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain 2000; 85: 317-32.

14. Linton SJ. The relationship between activity and chronic back pain. Pain 1985; 21: 289-94.

15. Turk DC, Rudy TE. Persistent pain and the injured worker: Integrating biomedical, psychosocial and behavioral factors. J Occup Rehab 1991; 1: 159-79.

16. Turk DC, Flor H. Chronic Pain: A biobehavioral perspective. In: Gatchel RJ, Turk DC, eds. Psychosocial Factors in Pain. New York, Guilford Press, 1999.

17. Marbach JJ, Hulbrock J, Hohn C, Segal AG. Incidence of phantom tooth pain: an atypical facial neuralgia. Oral Surg Oral Med Oral Pathol 1982; 53: 190-3.

18. Wren RW. Potters New Encyclopedia of Botanical drugs and Preparations, 5th impression. Northamptonshire, Health Science Press, 1973.

19. Phatak SR. Materia Medica of Homeopathic Medicines, 2nd ed. New Delhi, Indian Books and Periodicals Syndicate, 1977.

20. Kent JT. Repertory of the Homoeopathic Materia Medica with Word Index, 5th ed. New Delhi, B. Jain Publishers, 1987.

21. Harris M. Psychogenic aspects of facial pain. Br Dent J 1974; 136: 199-202.

22. Mahan PE, Alling CC. Facial Pain. Philadelphia, Lea & Febiger, 1991, pp. 304-5.

23. Epstein JB, Grushka M, Le N. Topical clonidine for orofacial pain: a pilot study. J Orofac Pain 1997; 11: 346-52.

24. Lauritano D, Spadari F, Formaglio F, Zambellini Artini M, Salvato A. Etiopathogenic, clinical-diagnostic and therapeutic aspects of the burning mouth syndrome. Research and treatment protocols in a patient group. Minerva Stomatologica 1998; 47: 239-51.

25. Smith WC, Bourne D, Squair JO, Phillips D, Alastair Chambers W. A retrospective cohort study of post mastectomy pain syndrome. Pain 1999; 83: 91-5.

26. Brooker C, Cousins MJ, Molloy AR. Neuropathic pain: a GP's guide. Mod Med 1999; 42: 58-67.

27. Loeser JD. Herpes zoster and postherpetic neuralgia. Pain 1986; 25: 149-64.

28. Carter GT, Jensen MP, Galer BS, Kraft GH, Crabtree LD, Beardsley RM, Abresch RT, Bird TD. Neuropathic pain in Charcot-Marie-Tooth disease. Arch Phys Med Rehab 1998; 79; 1560-4.

29. Mogil JS, Grisel JE. Transgenic studies of pain. Pain 1998; 77: 107-28.

30. Campbell RL, Parks KW, Dodds RN. Chronic facial pain associated with endodontic therapy. Oral Surg Oral Med Oral Pathol 1990; 69: 287-90.

31. Nicolodi M, Sicuteri F. Phantom tooth diagnosis and an anamnestic focus on headache. N Y State Dent J 1993; Dec: 35-7.

32. Allerbring M, Haegerstam G. Characteristics of patients with chronic idiopathic orofacial pain. Acta Odontol Scand 1993; 51: 53-8.

33. Vickers ER, Cousins MJ, Woodhouse A. Pain description and severity of chronic orofacial pain conditions. Aust Dent J 1998b; 43: 403-9.

34. Yontchev E, Carlsson GE, Hedegård B. Clinical findings in patients with orofacial discomfort complaints. Int J Oral Maxillofac Surg 1987; 16: 36-44.

35. Fishbain DA, Trescott J, Cutler B, Abdel-Moty E, Steele Rosomoff R, Rosomoff HL. Do some chronic pain patients with atypical facial pain overvalue and obsess about their pain ? Psychosomatics 1993; 34: 355-9.

36. Aghabeigi B, Feinmann C, Harris M. Prevalence of post-traumatic stress disorder in patients with chronic idiopathic facial pain. Br J Oral Maxillofac Surg 1992; 30: 360-4.

37. Pither CE, Nicholas MK. The identification of iatrogenic factors in the development of chronic pain syndromes: abnormal treatment behaviour? In: Bond MR, Charlton JE, Woolf CJ, eds. Proc VIth World Congress on Pain. New York, Elsevier, 1991, 429-34.

38. Siddall PJ, Cousins MJ. Introduction to pain mechanisms: implications for neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. New York, Lippincott-Raven, 1998, pp. 675-714.

39. Levine JD, Fields HL, Basbaum AI. Peptides and the primary afferent nociceptor. J Neurosci 1993; 13: 2273-86.

40. Falcon M, Guendellman D, Stolberg A, Frenk H, Urca G. Development of thermal nociception in rats. Pain 1996; 67:203-8.

41. Martin WJ, Loo CM, Basbaum AI. Spinal cannabinoids are anti-allodynic in rats with persistent inflammation. Pain 1999; 82: 199-205.

42. Younger AS, Claridge RJ. The role of diagnostic block in the management of Morton's neuroma. Can J Surg 1998; 41: 127-30.

43. Vickers ER, Cousins M. Neuropathic orofacial pain. Part 1: Prevalence and pathophysiology. Aust Endod J 2000; 26: 19-26.

44. Vickers ER, Cousins M. Neuropathic orofacial pain. Part 2: Diagnostic procedures, treatment guidelines and case reports. Aust Endod J 2000; 26: 53-63.

45. Janig W, McLachlan EM. Characteristics of function-specific pathways in the sympathetic nervous system. TINS 1992; 15: 475-81.

46. Habler H, Eschenfelder S, Liu XG, Janig W. Sympathetic-sensory coupling after L5 spinal nerve lesion in the rat and its relation to changes in dorsal root ganglion blood flow. Pain 2000; 87: 335-45.

47. Walker SM, Cousins MJ. Complex regional pain syndromes: including "reflex sympathetic dystrophy" and "causalgia". Anaesth Intensive Care 1997; 25: 113-25.

48. Berkley KJ. Sex differences in pain. Behav Brain Sci 1997; 20: 371-80.

49. Von Korff M, Dworkin SF, Le Resche L. Graded chronic pain status: an epidemiologic evaluation. Pain 1990; 40: 279-91.

50. Berkley KJ, Holdcroft A. Sex and gender differences in pain. In: Wall PD, Melzack R, eds. Textbook of Pain, 4th ed. London, Churchill Livingstone, 1999, pp. 951-66.

51. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. Kappa-opioids produce significantly greater analgesia in women than in men. Nature Med 1996; 2: 1248-50.

52. Akesson TR, Micevych PE. Endogenous opioid-immunoreactive neurons of the ventromedial hypothalamic nucleus concentrate estrogen in male and female rats. J Neurosci Res 1991; 28: 359-66.

53. Shughrue PJ, Dorsa DM. Gonadal steroids modulate the growth-associated protein GAP-43 (neuromodulin) mRNA in postnatal rat brain. Brain Res Develop Brain Res 1993; 73: 123-32.

54. Fowler-Kerry S, Lander J. Assessment of sex differences in children's and adolescents' self-reported pain from venipuncture. J Pediatr Psychol 1991; 16: 783-93.

55. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain 2000; 87: 325-34.

56. National Health and Medical Research Council. Acute Pain Management: Scientific Evidence. Canberra, AusInfo, 1998, pp. 11-2.

57. Presley RW, Cousins MJ. Current concepts in chronic pain management. Curr Ther 1992; 18: 51-60.

58. McGrath PA. The measurement of human pain. Endod Dent Traumatol 1986; 2: 124-9.

59. Sriwatanakul K, Kelvie W, Lasagna L, Calimlim JF, Weis OF, Mehta G. Studies with different types of analogue scales for measurement of pain. Clin Pharmacol Ther 1983; 34: 234-9.

60. Seymour RA, Simpson JM, Charlton JE, Phillips ME. An evaluation of length and end-phrase of visual analogue scales in dental pain. Pain 1985; 21: 177-85.

61. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983; 17: 45-56.

62. Van Buren J, Kleinknecht RA. An evaluation of the McGill Pain Questionnaire for use in dental pain assessment. Pain 1979; 6: 23-33.

63. Grushka M, Sessle BJ. Applicability of the McGill Pain Questionnaire to the differentiation of 'toothache' pain. Pain 1984; 19: 49-57.

64. Seymour RA, Charlton JE, Phillips ME. An evaluation of dental pain using visual analogue scales and the McGill Pain Questionnaire. J Oral Maxillofac Surg 1983; 41: 643-8.

65. Melzack R, Terrence C, Fromm G, Ansel R. Trigeminal neuralgia and atypical facial pain: use of the McGill Pain Questionnaire for discrimination and diagnosis. Pain 1986; 27: 297-302.

66. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975; 1: 277-99.

67. Vickers ER, Punnia-Moorthy A. A comparison of the efficacy of three topical anaesthetic agents. Aust Dent J 1992; 37: 266-70.

68. Vickers ER, Marzbani N, Gerzina TM, McLean C, Punnia-Moorthy A, Mather LE. Pharmacokinetics of EMLA cream 5% application to oral mucosa. Anesth Prog 1997; 44: 32-7.

69. Donkor P, Wong J, Punnia-Moorthy A. An evaluation of the closed mouth mandibular block technique. Int J Oral Maxillofac Surg 1990; 19: 216-9.

70. Gow-Gates GA. The Gow-Gates mandibular block: regional anatomy and analgesia. Aust Endod J 1998; 24:18-9.

71. Sisk AL. Evaluation of the Akinosi mandibular block technique in oral surgery. J Oral Maxillofac Surg 1986; 44:113-5.

72. Cruz EV, Quengua JB, Gutierrez IL, Abreu MA, Uy HG. A comparative study: classical, Akinosi, and Gow-Gates techniques of mandibular nerve block. J Philippine Dent Assoc 1994; 46:13-9.

73. Saxen MA, Adams WR, Splonik KS, Campbell RL. Diagnostic lidocaine infusion in patients with chronic orofacial pain. Anesth Prog 1994; 41: 12416-256 (abstract).

74. Gratt BM, Sickles EA, Graff-Radford SB, Solberg WK. Electronic thermography in the diagnosis of atypical odontalgia: a pilot study. Oral Surg Oral Med Oral Pathol 1989; 68: 472-81.

75. Graff-Radford SB, Ketelaer MC, Gratt BM, Solberg WK. Thermographic assessment of neuropathic facial pain. J Orofac Pain 1995; 9: 138-45.

76. Bonica JJ. Causalgia and other reflex sympathetic dystrophies. In: Bonica JJ, ed. The Management of Pain. Pennsylvania, Lea & Febiger, 1990, pp. 220-43.

77. Raja SN, Treede R, Davis KD, Campbell JN. Systemic alpha-adrenergic blockade with phentolamine: a diagnostic test for sympathetically maintained pain. Anesthesiol 1991; 74: 691-8.

78. Diamond AW, Coniam SW. The Management of Chronic Pain. Oxford, Oxford University Press, 1991, pp. 101-59.

79. Rosenberg JM, Harrell C, Ristic H, Werner RA, de Rosayro AM. The effect of gabapentin on neuropathic pain. Clin J Pain 1997; 13: 251-5.

80. Gillin S, Sorkin LS. Gabapentin reverses the allodynia produced by the administration of anti-GD2 ganglioside, an immunotherapeutic drug. Anesth Analg 1998; 86: 111-6.

81. Attal N, Brasseur L, Parker F, Chauvin M, Bouhassira D. Effects of gabapentin on the different components of peripheral and central neuropathic pain syndromes: a pilot study. Eur Neurol 1998; 40: 191-200.

82. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain 1997; 73: 123-39.

83. Stanberry LR, Bourne L, Bravo FJ, Bernstein DI. Capsaicin-sensitive peptidergic neurons are involved in the zosteriform spread of herpes simplex virus infection. J Med Virol 1992; 38: 142-6.

84. Rowbotham MC. Topical analgesic agents. In: Fields HL, Liebeskind JC, eds. Pharmacological Approaches to the Treatment of Chronic Pain: New Concepts and Critical Issues. Progress in Pain Research and Management, Vol 1, Seattle, IASP Press, 1994, pp. 211-28.

85. Epstein JB, Marcoe JH. Topical application of capsaicin for treatment of oral neuropathic pain and trigeminal neuralgia. Oral Surg Oral Med Oral Pathol 1994; 77: 135-40.

86. Dao TTT, Lavigne GJ, Charbonneau A, Feine JS, Lund JP. The efficacy of oral splints in the treatment of myofascial pain of the jaw muscles: a controlled clinical trial. Pain 1994; 56: 85-94.

87. Vickers ER, Cousins M, Nicholas M. Facial pain: a biopsychosocial problem. Medicine Today 2000; 11: 42-8.

88. Waddell G, Bircher M, Finlayson D, Main CJ. Symptoms and signs: physical disease or illness behaviour? Br Med J 1984; 289: 739-41.

89. Rudy TE. Psychophysiological assessment in chronic orofacial pain. Anesth Prog 1990; 37: 82-7.

90. Fordyce WE, Lansky D, Calsyn DA, Shelton JL, Stolov WC, Rock DL. Pain measurement and pain behavior. Pain 1984; 18: 53-69.

91. Blumer D, Heilbronn M. The pain-prone disorder: a clinical and psychological profile. Psychosomatics 1981; 22: 395-402.

92. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical Care 1992; 30: 473-83.

93. Beck AT, Ward CH, Mendelson M, Mock N, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatr 1961; 4: 561-71.

94. Nicholas MK, Wilson PH, Goyen J. Comparison of cognitive-behavioral group treatment and an alternative non-psychological treatment for chronic low back pain. Pain 1992; 48 : 339-47.