CHAPTER 1

STUDY 1: PAIN INTENSITY AND PAIN DESCRIPTION OF CHRONIC OROFACIAL PAIN CONDITIONS

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1.1 Introduction

Patients with chronic orofacial pain often present to pain clinics with an extensive history of investigations and procedures. There is general agreement among practitioners that the differential diagnosis of chronic orofacial conditions is often difficult (Bennett and Sessle, 1990). Pain in this region can be “severe” (National Health and Medical Research Council, 1988), yet few studies have been published to assist multidisciplinary pain clinics in arriving at a diagnosis for these patients. In addition, the prevalence of orofacial pain and associated symptoms appears to be relatively common in the general population (Gordon *et al.*, 1983; Crook *et al.*, 1984; Marciani, Haley and Roth, 1985). For example, 12.6% of females in an epidemiological study by Jensen, Rasmussen *et al.*, (1993) were shown to manifest at least three or more signs and symptoms of temporomandibular disorder (TMD). A more recent study indicated that 30% of the general population experienced TMD, with 5% of the survey claiming “moderate to severe pain” from the disorder (Goulet, Lavigne and Lund, 1995).
A precise diagnosis pertaining to chronic pain of the orofacial region requires consideration of the complex local anatomy of the head and neck region, involving sensory nerve distribution, local musculature (muscles of mastication, muscles of facial expression, neck muscles), salivary gland dysfunction and the intricate translatory mechanism of the temporomandibular joint. In addition, pain states (e.g. neuropathic pain) that may be unfamiliar to clinicians are present in the orofacial region (Epstein and Marcoe, 1994). While specific pharmacological tests are available to assess components of chronic pain, often these tests can only be carried out in specialist pain centres. Psychological factors can figure prominently in chronic pain, and AFP would be currently classified as “pain of psychogenic origin” by the IASP (Merskey et al., 1994). In addition, “stress” is very frequently reported in patients with TMD (Aghabeigi, Feinmann and Harris, 1992) and other chronic pain conditions (Schleifer, Marbach and Keller, 1990). The description of a pain condition and the patient’s reported pain intensity can provide valuable information for diagnosis and can consequently alert the general dental practitioner as to when referral is appropriate. The multidisciplinary approach to diagnosis and management of these patients is highly recommended, and consequently, the use of standard pain measuring instruments such as the visual analogue scale (VAS) and the MPQ are necessary for quantitating baseline pain intensity. However, documentation on the usefulness of these instruments for chronic orofacial pain assessment is scarce.

Pencil and paper instruments are universally recognised and widely used. Such instruments include the VAS for measuring pain intensity, and the MPQ for pain measurement that uses a global analysis incorporating sensory, affective and temporal pain qualities. McGrath
(1986), an experienced pain researcher, proposed that analogue scales have reliability, validity and versatility. Variations of the VAS exist and a comparison of analogue scales found graded linear scales more reliable than descriptive analogue scales (Sriwatanakul, Kelvie et al., 1983). Seymour and coworkers (Seymour, Simpson et al., 1985) evaluated various length and end-phrase variations of the VAS and found the 10 cm VAS had the smallest measurement error, while the end-phrase “worst pain imaginable” had the greatest sensitivity in measuring “present pain” in a group (n = 100) suffering dental pain. The VAS is useful for both chronic and experimental pain (Price, McGrath et al., 1983).

The MPQ has been used for evaluating acute (post-operative) orofacial pain from third molar teeth removal (Van Buren and Kleinknecht, 1979). Grushka and Sessle (1984) assessed acute “toothache” patients using the MPQ to differentiate different stages of pulpitis (irreversible versus reversible), with a correct prediction rate of 73% in subjects. Similar findings have been reported in using the MPQ to differentiate pulpitis from pericoronitis (Seymour, Charlton and Phillips, 1983). Only one study, however, has used the MPQ for analysing chronic orofacial pain conditions (Melzack, Terrence et al., 1986). In this study, the authors evaluated two chronic orofacial pain conditions [AFP and trigeminal neuralgia (TN)] from which they correctly predicted the diagnosis in 90% of patients, indicating the value of the instrument. However, patients suffer from two other frequently encountered chronic orofacial pain conditions when referred to a pain clinic (TMD and AO, data from this study), that have not been subjected to VAS / MPQ analyses. Surprisingly, assessment of the relationship between VAS and components of the
MPQ has been limited (Reading, 1980), although these instruments would be, arguably, the most frequently used measuring tools in clinical and laboratory-induced pain.

1.2 Aims

There were several aims for this analysis of chronic orofacial pain:

1. to analyse general data and pain variables for any significant links between gender, age, duration of pain, temporal quality of pain, and pain intensity from diagnosed chronic orofacial pain conditions;

2. to establish if any significant inter-relationships exist between MPQ and VAS measures for chronic orofacial pain; and

3. to examine the frequency of single versus multiple concurrent chronic orofacial pain complaints encountered in this study using case studies of patients with a primary diagnosis of AO to illustrate this point.

1.3 Patients and methods

This study was carried out on 120 consecutive patients with chronic orofacial pain from a multidisciplinary pain clinic patient population at the Pain Management and Research Centre, University of Sydney (the investigator’s institution). Subjects were referred by medical and dental practitioners, with the main patient complaint being persistent pain in the orofacial region. The large majority of patients had previously sought both medical and dental treatment in respect of their pain, prior to attendance at the pain clinic. The diagnosis of each subject’s pain condition was made by the investigator (an oral surgeon), in collaboration with other pain centre personnel (anaesthetist / pain specialist, psychologist,
psychiatrist and physiotherapist). The diagnoses were based on the criteria specified by the IASP (Merskey, 1986; Merskey et al., 1994). A diagnosis that included TMD was based on combined clinical examination findings and subjective patient symptom reporting (Truelove, Sommers et al., 1992). For this study, several well defined pathological conditions, such as TN and osteoarthritis, were included in one pathology group (Path) for the purposes of statistical analyses. All patients completed a comprehensive questionnaire that included age, sex, pain duration and temporal qualities of pain (constant, periodic, transient). Patients usually completed the questionnaire at home to allow ample time for completion, prior to their first appointment. Patients were advised that interpreter services were available if needed, although no patient requested this form of assistance.

Pain measurement utilised the VAS and MPQ. The VAS was 10 cm in length, with ends anchored “no pain” and “worst pain imaginable”. The written instruction above the scale was “Please mark your level of pain”. Where a patient indicated a variable pain score (e.g. 5-7), then the midpoint was taken (VAS = 6) for statistical analysis. The MPQ was the standard form designed by Melzack (1975) and consisted 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 were scored and ranked to furnish four indices of pain quality: (i) Pain Rating Index of Sensory descriptors [PRI(S)], (ii) Pain Rating Index of Affective descriptors [PRI(A)], (iii) Pain Rating Index of Evaluative descriptors [PRI(E)], and (iv) Pain Rating Index of Miscellaneous descriptors [PRI(M)]. The four pain rating scores of each patient correctly completing the questionnaire were then added to give a fifth index, the Total Pain Rating Index [PRI(T)].
The written instruction above the MPQ was “Some of the words below describe your present pain. Circle only those words that best describe it. Leave out any category that is not suitable. Use only a single word in each category - the one that applies best.” Subjects indicating more than one word per group were excluded during statistical analyses, but were included in Table 1.6 (Frequency of pain descriptors in chronic orofacial pain conditions) to illustrate the usefulness of the MPQ in aiding the diagnosis of relevant conditions.

Statistical analyses

One-way analysis of variance (ANOVA) followed by Tukey pairwise comparison, student's $t$ test, Kruskal-Wallis nonparametric analysis of variance, chi-squared test and Pearson's $r$ were used where appropriate.

1.4 Results

Subjects ranged in age from 16-87 years (mean = 52 years, S.D. 16). Females outnumbered males in the study by 88 : 32, and for all pain conditions (Table 1.1). The most frequent condition diagnosed was AFP (n = 40), followed by TMD (n = 32), AO (n = 29), and pain arising from recognised pathological conditions of the orofacial region [(n = 19), Table 1.2]. However, both AFP and AO groups had substantial numbers of subjects who were diagnosed with a concurrent TMD problem. Results showed that the AFP group were diagnosed with either a single presenting complaint (AFP, n = 20) or a combined AFP-TMD complaint (n = 20). Similarly, AO was identified as a single complaint (AO, n = 12), or in association with TMD (AO-TMD, n = 17).
One subject incorrectly completed the VAS (a line was drawn past the 10 anchor with “10 million” written as a pain score) and nine subjects did not complete the VAS. Five subjects did not complete the MPQ and another 28 subjects completed the MPQ incorrectly.

Results of statistical analyses (VAS and MPQ)

Chi-squared test for gender analysis indicated there was a significantly greater number of females referred with chronic orofacial pain (P < 0.0001), and a significantly greater number of females diagnosed with AFP (P < 0.0001).

Pearson's r indicated a significant positive relationship between VAS and the Number of Words Chosen (NWC) index across all pain conditions ($R^2 = 0.186$, $P = 0.002$) (Figure 1.1). Student's $t$ tests indicated patients presenting with AFP-TMD reported significantly higher PRI(M) and PRI(T) scores (mean = 4.9, S.D. 2.8; mean = 26.5, S.D. 12.5, respectively) than patients presenting with AFP (mean = 2.4, S.D. 2.2; mean = 15.6, S.D. 8.5 respectively) ($P = 0.009$). ANOVA indicated that patients diagnosed with AFP reported significantly lower PRI(M) and PRI(T) scores ($P = 0.0005$) than patients presenting with TMD or pathology (Figures 1.2, 1.3).

Pearson's r indicated no relationship between VAS and pain duration, age or PRI(T). No significant differences were found between females and males on VAS, PRI(A) or PRI(S). In addition, all four pain conditions showed no significant difference between VAS or NWC.
1.5 Discussion

1.5.1 Gender differences

Females outnumbered males in the study group and in all pain conditions (Table 1.1); a similar gender difference in chronic orofacial pain groups have been reported by others (Gerschmann, Wright et al., 1987; Bush, Harkins et al., 1993). The detailed review by Bush et al., (1993) of TMD in 35 orofacial pain clinics showed similar findings of gender differences favouring greater female attendance (approximately 3:1, females : males). An explanation of the relationship between gender and pain has produced conflicting data. Lander and coworkers (Lander, Fowler-Kerry and Hill, 1990), showed that females have lower pain thresholds and lower pain tolerances than males in studies of experimental pain, and that women reported more physical symptoms (including pain) in clinical studies. However, Bush et al., (1993) demonstrated no significant difference in experimental pain (in both pain patients and pain-free patients) based on gender. Similarity of pain intensity scores in males and females have been reported for acute (post-extraction) dental pain (Van Buren et al., 1979; Sisk, Grover and Steflik, 1991) and chronic orofacial pain (TMD) from this study and others (Bush et al., 1993). It has been proposed that gender differences in pain may possibly result from neuronal function influenced by hormonal variation, including activation of endogenous analgesic systems (McGrath, 1994), while others have found a higher incidence of females who “actively” seek treatment for health complaints, including orofacial pain (Feinmann, 1983). In summary, however, no definitive reason has yet been shown for gender difference in chronic orofacial pain, despite the common findings from a number of studies.
The presence of the youngest patient (female, 16 years old with pathology of the mandibular condyle; Table 1.2), and the only teenager, in this study, shows that chronic orofacial pain does not appear prevalent in the young age group and confirms the low incidence (4.3% of patients in an orofacial pain clinic younger than 15 years) from previous data (Klausner, 1994). Psychological, environmental, biochemical and genetic factors would most likely be involved in limiting chronic pain mechanisms in this group, but substantial investigation is needed to define the possible influence of these modulating factors in the younger age group.
TABLE 1.1
Primary Diagnosis of Chronic Orofacial Pain Conditions

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>No. of Males (n = 32)</th>
<th>No. of Females (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>b 6</td>
<td>b 34</td>
</tr>
<tr>
<td>TMD</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>AO</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>recognised pathological conditions (Path)</td>
<td>4</td>
<td>15</td>
</tr>
</tbody>
</table>

\(^{a,b}\) Chi-squared statistically significant at P < 0.0001 for gender difference
TABLE 1.2

Diagnosis of Pathological Conditions (n = 19)

<table>
<thead>
<tr>
<th>Pathological Condition</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>arthritis / pathology of temporomandibular joint</td>
<td>5</td>
</tr>
<tr>
<td>trigeminal neuralgia</td>
<td>5</td>
</tr>
<tr>
<td>facial neuropathic pain</td>
<td>4</td>
</tr>
<tr>
<td>burning tongue syndrome</td>
<td>2</td>
</tr>
<tr>
<td>maxillary sinusitis</td>
<td>2</td>
</tr>
<tr>
<td>anaesthesia dolorosa</td>
<td>1</td>
</tr>
</tbody>
</table>
**Figure 1.1**
Significant positive correlation between VAS and NWC ($R^2 = 0.186$, $P = 0.002$) in patients correctly completing MPQ and VAS ($n = 82$). Scatterplot represents each patient score (VAS versus NWC) with line of best fit transecting origin.
Figure 1.2
Scatterplots of the distribution of PRI(T) scores with significant difference between AFP group and AFP-TMD, TMD and Pathology groups.
Figure 1.3
Scatterplots of the distribution of PRI(M) scores with significant difference between AFP group and AFP-TMD, TMD and Pathology groups.
1.5.2 Severity of chronic orofacial pain

Perhaps the most important finding of this study was the severity of chronic orofacial pain conditions as measured by the MPQ. TMD, a frequently encountered condition in the general population, had a mean score of 26.8 on the PRI(T) and scores higher than back pain (26.3), cancer pain (26.0) and phantom pain (25.0) (Melzack, 1975). It is noteworthy that 65% of the subjects in this study exhibited TMD as either a primary or secondary condition. The high mean pain score of TMD is only surpassed by the subjects with oral pathology (27.0), and by “psychiatric tension headache sufferers” (27.0) (Hunter and Philips, 1981). Patients diagnosed with AO (AO as a single condition and AO-TMD; mean = 22.6) and AFP (AFP as a single condition and AFP-TMD; mean = 21.0) scored higher than previously reported acute dental pain (19.5) (Grushka and Sessle, 1984), arthritis (18.8) and menstrual pain (17.5) (Melzack, 1975) (Table 1.3). A comparative rating of pain scores amongst the study group patients is shown in Table 1.4.

Data from this study also showed VAS pain intensity for TMD was the highest for any group (mean = 7.5, S.D. 1.7). However, another analysis of TMD (Bush et al., 1993) showed a lower mean pain intensity (females, mean = 3.8, S.D. 1.8; males, mean = 4.2, S.D. 1.8). Wilson and coworkers (Wilson, Dworkin et al., 1994) also reported that "high-intensity pain" (and heightened somatisation) were strong predictors of widespread TMD pain. Surprisingly, however, their "high-intensity pain" scored by VAS was only 3.5 (S.D. 2.6) for males and 2.6 (S.D. 1.1) for females, with a mean pain history for TMD of 5 years, reflecting the need for caution in both clinical and research situations in providing
subjective terms based on VAS measures. These lower VAS results could be explained by their methodology of using screening procedures, which was based on surveys of patients’ complaints in the general population. In contrast, the patients in this current study were directly referred to a pain centre, where higher levels of pain may be reasonably expected from active treatment-seeking patients. The source of patient recruitment (screening procedure or direct referral) in the study by Bush et al., (1993) was not mentioned.

Comparatively high pain scores from the orofacial region encountered in this study may be due to anatomical and psychological factors. For example, masticatory muscle pain has been related to clinical pain intensity of TMD (Raphael and Marbach, 1992). On a neural basis, there is a greater sensory nerve supply to the orofacial region (and hands) compared with other regions of the body (Tortora and Anagnostakos, 1990). The motor functions of speech, facial expression and masticatory muscles rely, in part, on sensory input for normal functioning. A recent report (Rath and Essick, 1990) reviewed previous literature assessing sensory innervation of the perioral region. In summary, Rath et al., (1990) found the anterior one-third of the tongue and perioral tissues, compared with the fingertips, possessed similar or greater spatial distribution for tactile detection, two-point discrimination and texture. In addition, the tongue and facial region are endowed with highly discriminating A-δ and C-fibre "warming" and "cooling" thermoreceptors. The dental pulp is particularly significant for the ability of its C-polymodal receptors to elicit pain despite a 'non-noxious stimulus'. Overall, for the same noxious stimulus, neural mechanisms clearly exist for 'greater sensory pain' of the oral cavity and perioral tissues, compared with other body regions.
Psychological and / or psychiatric factors may account for the high pain scores (as measured by both MPQ and VAS) encountered in this study. It is noteworthy, for example, that the highest rating chronic pain condition reported is "psychiatric tension headache" (Hunter et al., 1981). Studies have shown that psychiatric / psychological problems have a high incidence in patients attending dental pain clinics (Hughes, Hunter et al., 1989; Kinney, Gatchel et al., 1992). Of further note regarding orofacial pain is the concept of altered pain intensity and the spread of pain from the combined effect of nociception (spasm in the muscles of mastication) and the expression of pain such as grimacing (possible spasm in the muscles of facial expression). This involves a potential positive feedback loop between facial expression arising from ‘suffering’ and pain due to accentuated regional muscle contraction (Fiske and Ruscher, 1991). It is of interest that while “facial expression” has been shown to be a valid pain measuring instrument for infants (Craig, Prkachin and Grunau, 1992), it precludes itself for measuring adult ‘physiological’ pain, due to the likelihood of psychological overlays. These overlays would, from common human experience, include the ‘expectation of pain’ in human volunteer pain studies, and the range of facial expression to communicate ‘pain and suffering’ based on cultural influences.

Emotions such as sadness and anger are depicted by the muscles of facial expression as part of the ‘suffering component’ of chronic pain (Keefe, 1989). Also, developing traits associated with overt pain behaviour may be reflected by facial muscles. These traits, for example, may be demonstrated by a cynical attitude towards the medical establishment from failed therapy, and despair from restricted long term employment prospects. Price
(1988) showed high levels of "frustration" and "anger" in a group of patients with myofascial pain; similar findings of "frustration", "anger" and "anxiety" were reported in a more specific myofascial pain group (TMD) (Bush et al., 1993). Patients with TMD also show greater "catastrophizing" and "helplessness" scores; and lesser "coping" scores than healthy controls (Flor, Behle and Birbaumer, 1993), providing further evidence of cognitive aspects in orofacial pain patients. Three models examining the relationships between TMD and personality were summarised by Marbach (1992) in depicting the interplay of psychological, environmental and biochemical variables. Cooper and Cooper (1991) have described the extent of this complexity in diagnosing and treating TMD.

It is noteworthy that the majority of patients in this study exhibited TMD as a primary diagnosis (singular condition), or as a secondary diagnosis concurrent with another disorder. However, the concept that TMD should be classified as the secondary diagnosis for this study is only based on pain history, most subjects reporting the onset of TMD symptoms subsequent to the initial pain complaint. Considering the pain intensity scores of TMD, it should arguably be "the primary pain condition" by merit of comparing the relative pain score of its associated condition, in patients with a multiple diagnosis. Further evidence of parafunction and signs of functional disturbances were reported in patients with "oral discomfort" as a result of other dental pathology (Yontchev, Carlsson and Hedegård, 1987). It is unclear why a secondary TMD condition arises; however, one possible explanation may be the convergence of sensory and motor neurones in the head and neck region (Sessle, Hu et al., 1986). If bruxism proves to be a pain-coping mechanism for other chronic orofacial pain conditions, such as AO, then it may be of positive benefit in the
short term. However, any long term benefit would be negated through a worsening of the individual’s overall pain state by the subsequent development of secondary myofascial pain (TMD). Although there has been extensive documentation for TMD as a single patient complaint, its prevalence as a concurrent complaint from data in this study suggest that further investigation(s) with standardisation of clinical criteria and self-report instruments are warranted.

The study also demonstrated that pain intensity appeared to increase, the greater the area of pain. For example, TMD patients, in addition to severe facial and jaw pain, often presented with a wide extent of pain location involving the head, neck and shoulders. However, by definition, the pain region of AO and AFP is restricted to the oral cavity and face, and lower PRI(T) scores (mean = 18.0, S.D. 11.2; mean = 15.6, S.D. 8.5, respectively) were noted in this study. Differences in the temporal quality of pain were not found between the various conditions, although as expected, the majority of subjects suffering from TN experienced short term (transient or periodic) pain episodes (Table 1.5).
<table>
<thead>
<tr>
<th>Pain Condition</th>
<th>PRI(T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral pathology</td>
<td>27.0</td>
</tr>
<tr>
<td>“psychiatric” tension headache</td>
<td>27.0</td>
</tr>
<tr>
<td>TMD</td>
<td>26.8</td>
</tr>
<tr>
<td>AFP-TMD</td>
<td>26.5</td>
</tr>
<tr>
<td>back pain</td>
<td>26.3</td>
</tr>
<tr>
<td>cancer pain</td>
<td>26.0</td>
</tr>
<tr>
<td>AO-TMD</td>
<td>25.1</td>
</tr>
<tr>
<td>phantom limb pain</td>
<td>25.0</td>
</tr>
<tr>
<td>general practice tension headache</td>
<td>21.4</td>
</tr>
<tr>
<td>acute “toothache”</td>
<td>19.5</td>
</tr>
<tr>
<td>arthritis</td>
<td>18.8</td>
</tr>
<tr>
<td>AO</td>
<td>18.0</td>
</tr>
<tr>
<td>menstrual pain</td>
<td>17.5</td>
</tr>
<tr>
<td>AFP</td>
<td>15.6</td>
</tr>
</tbody>
</table>

- Vickers (this study)
- Melzack (1975)
- Grushka and Sessle (1984)
<table>
<thead>
<tr>
<th>Condition</th>
<th>VAS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>NWC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PRI(M)</th>
<th>PRI(T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO</td>
<td>6.7 (2.3)</td>
<td>7.4 (4.0)</td>
<td>3.8 (3.8)</td>
<td>18.0 (11.2)</td>
</tr>
<tr>
<td>AO-TMD</td>
<td>7.0 (1.6)</td>
<td>10.4 (4.1)</td>
<td>4.9 (3.0)</td>
<td>25.1 (9.0)</td>
</tr>
<tr>
<td>AFP</td>
<td>6.7 (2.5)</td>
<td>6.8 (2.8)</td>
<td>2.4 (2.2)&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
<td>15.6 (8.5)&lt;sup&gt;e,f,g&lt;/sup&gt;</td>
</tr>
<tr>
<td>AFP-TMD</td>
<td>7.3 (2.0)</td>
<td>10.6 (5.9)</td>
<td>4.9 (2.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26.5 (12.5)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>oral pathology</td>
<td>7.1 (2.0)</td>
<td>10.8 (4.6)</td>
<td>6.7 (2.8)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27.0 (12.3)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>TMD</td>
<td>7.5 (1.7)</td>
<td>10.4 (5.1)</td>
<td>5.8 (4.3)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>26.8 (14.1)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Positive correlation (Pearson’s r) between VAS and NWC; P = 0.002

<sup>b,e</sup> Student’s t test statistically significant for PRI(M) and PRI(T); P = 0.009

<sup>c,d,f,g</sup> ANOVA statistically significant for PRI(M) and PRI(T); P = 0.0005
**TABLE 1.5**

Temporal Qualities of Pain Conditions (n = 118)

<table>
<thead>
<tr>
<th>Temporal Quality</th>
<th>AO (n = 29)</th>
<th>AFP (n = 39)</th>
<th>TMD (n = 31)</th>
<th>Pathology (n =19)</th>
</tr>
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<tbody>
<tr>
<td>constant</td>
<td>24</td>
<td>35</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>periodic</td>
<td>5</td>
<td>4</td>
<td>8</td>
<td>4 (TN, n = 2)</td>
</tr>
<tr>
<td>intermittent</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (TN, n = 2)</td>
</tr>
</tbody>
</table>
1.5.3 Clinical aspects and parameters of using VAS / MPQ and inter-instrument relationships

The VAS is generally considered to be a simple and reliable pain measuring instrument for patients. However, this study showed one subject incorrectly completed the VAS (a line was drawn past the 10 anchor with “10 million” written as a pain score) and 8% of subjects did not complete the VAS; similar results have been reported by Kremer, Atkinson and Ignelzi (1981) with 11% of respondents not completing the VAS. Although the scale has internally consistent ratio scale properties in experimental and chronic pain (Price, Bush et al., 1994), the instrument limits the patient to express his / her “usual” level of pain. However, pain intensity can vary markedly over time and activities, as illustrated by daily log charts, and this deficiency of the VAS was the main reason given by non-responders.

In this study, 32% of subjects did not attempt, or incorrectly completed the MPQ. Several patients who did not attempt to complete the MPQ stated their reasons as: “it was too involved”, or “did not feel that the questionnaire could express the pain adequately”. The majority of patients who incorrectly completed the MPQ claimed that the questionnaire could not be completed in the way designed (i.e. only one word descriptor per group). The most frequently volunteered response from these patients was that their pain often “varied”, and therefore, two or more words were chosen from within the word group. Unfortunately, this constraint of the MPQ precludes the use of substantial patient data in statistical analysis. The limitation of “one word per group” needs further deliberation by pain researchers, perhaps allowing mean rank values in a word group, where more than one
word is selected. While the MPQ provides valuable information for clinical pain assessment, this constraint reduces the research productivity of the MPQ. While VAS scores were similar for pain conditions in this study, the MPQ analysis showed a significant difference in various aspects that may prove valuable in diagnosis and treatment. Results showed particular MPQ scales were discriminant in comparing a single pain condition from a multiple pain complaint; AFP to AFP-TMD showed an increase in the PRI(M) and PRI(T). This suggests that the MPQ has diagnostic capability in relation to determining single versus multiple pain conditions. Reading (1980) has previously reported a correlation between VAS and sensory word descriptors, while this study showed a significant correlation between the VAS and NWC index of the MPQ. While most published studies report PRI scales, this study found NWC to be extremely useful. In future, patient assessment for pain intensity may be more accurately portrayed using the frequency of individual word descriptors reported (Reading, 1980, 1982), and NWC (this study), than PRI indices.

An advantage of pain research in the orofacial region is the comparison of data of acute and chronic pain from the same anatomical location. For example, an MPQ analysis of acute “toothache” found only three descriptors were chosen by more than one-third of patients: “tender” (36%) and “annoying” (41%) for reversible pulpitis; “tender” (35%) and “sharp” (40%) for irreversible pulpitis (Grushka et al., 1984). In contrast, data from this study for chronic conditions showed subjects with AO-TMD (n = 17) listed nine descriptors, AFP-TMD (n = 20) listed ten descriptors, and those with pathology (n = 18) listed seven descriptors (Table 1.6). AO has been described as “phantom tooth pain”
(Marbach, 1978, 1993a, 1993b, 1993c; Marbach, Hulbrock et al., 1982); however, the underlying mechanism(s) in the development of AO is unclear. The increased number of pain descriptors and increased pain intensity, from “acute toothache” to “chronic toothache - phantom tooth pain” (AO), may serve as a viable epidemiological and clinical model in observing the progression of acute inflammatory states to neuropathic pain conditions (such as AO). Furthermore, data from this study also suggest the potential diagnostic value of NWC in the progression of acute to chronic pain in prospective clinical trials. Currently, the accepted definition of chronic pain is pain present for more than three months. This definition, an arbitrary decision based on a time continuum, does not take into account background medical conditions (such as diabetes) and events affecting the individual’s psychological state. Turk (1997) has reviewed the available data in analysing the transition of acute to chronic pain (predominantly back pain). Several variables were identified as strong predictors of transition - pain severity, and alcohol and substance abuse. Considering the high pain scores from orofacial pain conditions, both the MPQ and VAS may serve as simple, yet important, instruments in attempting to predict the outcome of acute pain, and thus, the early intervention of chronic pain management strategies.

1.5.4 Complexity of diagnosis: the prevalence of two or more concurrent chronic orofacial pain conditions

As previously mentioned, results from this study showed that 65% of patients were diagnosed with more than one pain condition of the orofacial region. Two case studies are presented with a primary diagnosis of AO to illustrate this point, followed by a discussion of the difficulties of diagnosing chronic orofacial pain among medical and dental disciplines.
**Case Study 1 AO:** A 58 year old female had a one year history of pain that was located in the maxilla. Intraorally, the pain extended from the upper left third molar region to the upper right canine region, and radiated to the left cheek. The patient claimed the onset of pain occurred following extraction of the upper left third molar complicated by a dry socket. There were no other areas of pain in the body. The pain was increased in severity by many modalities including exercise, weather changes, tension, stress and noise. The pain was rated as 10/10 on the VAS and MPQ pain descriptors listed were “pulsing, throbbing, nagging, dreadful” qualities. The pain was “constant and severe”. There was no evidence of an associated TMD, based on clinical examination and self-report questionnaire.

**Case Study 2 AO-TMD:** A 23 year old male, final year medical student reported a three year pain history. The pain occupied the lower left quadrant (lower left second and third molar region) and had spread to the upper left quadrant (upper left third molar region). The onset of pain followed the removal of the lower left third molar. Over time, the pain extended to include the left side of the face and left neck region. The pain varied between 1-8/10 on the VAS, and MPQ descriptors listed were “throbbing, sharp, tugging, tingling, aching, taut, tiring, punishing, intense, spreading, tight, cold, dreadful” qualities. The patient listed a number of signs and symptoms indicative of TMD - neck pain, facial muscle tension, bruxism, teeth chipping, sinusitis-like symptoms, tingling sensation in face.

**Discussion of Case Studies:** Few studies investigating chronic orofacial pain have suggested multiple pain states (Benoliel, Eliav et al., 1994); the large majority of studies specifically label a patient with only one diagnosis. A potential source of an insufficient
diagnosis (i.e. a patient diagnosed with one condition but suffering from multiple pain conditions) is that the region of orofacial pain is treated by dental and medical disciplines. For example, a patient may be diagnosed with TN by a neurologist, but a secondary TMD that may be present is not recognised. This is further complicated by the historical differences that persist in definitions and criteria of orofacial pain conditions such as TMD, AO and AFP among pain specialists, dental specialists and neurologists (Sjaastad, 1988; Heft and Rugh, 1990; Merskey et al., 1994). Pain of the orofacial region is perhaps unique, in that various medical and dental disciplines are responsible for diagnosis and treatment of disorders in this region. Acute dental pain, maxillary sinus pain from infection and organic neurological disorders of the face are routinely assessed by the respective dental practitioner, medical practitioner / otolaryngologist and neurologist / neurosurgeon. However, chronic pain of the orofacial region is not unlike other anatomical regions with chronic pain; it may involve neural mechanisms, vascular and musculoskeletal components, and psychological factors. It is essential that investigators involved in studies of orofacial pain have, at least, the knowledge of different criteria from specialty groups. The adoption of a single taxonomy for pain among health practitioners, irrespective of background discipline, is to be encouraged.

**TABLE 1.6**

**Frequency of MPQ Pain Descriptors**

(Frequency expressed as % of group and only listed when indicated by more than one-third of the patients in each category)
<table>
<thead>
<tr>
<th>Descriptor</th>
<th>AO (n = 11)</th>
<th>AO-TMD (n = 17)</th>
<th>AFP (n = 17)</th>
<th>AFP-TMD (n = 20)</th>
<th>Pathology (n = 18)</th>
<th>TMD (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>throbbing</td>
<td>33</td>
<td>59</td>
<td>37</td>
<td>57</td>
<td>34</td>
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<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sharp</td>
<td>33</td>
<td>41</td>
<td></td>
<td>42</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>burning</td>
<td></td>
<td></td>
<td></td>
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<td>37</td>
<td>50</td>
</tr>
<tr>
<td>tender</td>
<td>33</td>
<td>53</td>
<td></td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tiring</td>
<td></td>
<td>35</td>
<td></td>
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<tr>
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<td>33</td>
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<td></td>
<td>47</td>
<td></td>
<td>43</td>
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</tr>
<tr>
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<td></td>
<td>52</td>
<td>68</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>radiating</td>
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<td></td>
<td></td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dreadful</td>
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<td></td>
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</tbody>
</table>

### 1.6 Conclusion

The MPQ was designed to assess the global impact of pain as a response to the limitations of the VAS. Both the MPQ and VAS are relatively simple instruments that provide valuable data for assessing and managing the patient with orofacial pain. However, both
instruments require cognitive ability and are not useful in specific patient groups such as infants, the mentally handicapped, and migrants with limited knowledge and understanding of pain terms in the host country. Nevertheless, both the VAS and MPQ serve as non-invasive pain measuring tools that are easily completed by the patient. Multiple scores can be recorded over time for baseline pain intensity and subsequent analgesic efficacy. The instruments are widely used, and have considerable published documentation, for comparison, in prospective studies. The MPQ and VAS are widely accepted as the most useful way of conveying information between patient and health practitioner at the current time.

Based on the results of this study, the majority of patients suffering from chronic orofacial pain have “constant” pain. The intensity of pain in this region is similar to other chronic pain conditions such as back pain, cancer pain and arthritis. It has been witnessed by the investigator that several patients from this orofacial pain cohort claimed that the “constant” and “severe” nature of pain experienced caused life-threatening (high suicide risk or attempted suicide) situations, underlying the serious impact of pain. The puzzling nature of concurrent pain conditions often confounded the referring practitioner who was unable to arrive at a diagnosis. In addition, the nature of pain referral, and indeed patient referral itself, among disciplines such as ear, nose and throat surgeons, neurologists and dental surgeons also make for a diagnosis that is difficult and potentially delayed. Delayed diagnosis can, and often does, prolong subsequent treatment resulting in diminishingly successful outcomes. In summary, orofacial pain may be exceedingly complex, being based on anatomical and psychological factors, as well as poorly understood variables such as
gender, and complex biochemical events and neurophysiological mechanisms involved in the pathophysiology of chronic pain.
CHAPTER 2

STUDY 2: ATYPICAL FACIAL PAIN: A CONTENTIOUS DEFINITION, AND GUIDELINES FOR DIAGNOSIS AND TREATMENT

Published in part as:


2.1 Introduction

Definition of atypical facial pain

The term AFP has a chequered history in the IASP taxonomy of pain terms and definitions. For example, AFP was listed as an orofacial pain condition in the handbook in 1986 (Merskey, 1986) but not listed or referred to in any way in the 1994 revised taxonomy (Merskey et al., 1994). Arguably, the closest definition of AFP in the 1994 taxonomy would fall within the general classification of "pain of psychological origin: hysterical or hypochondriacai". Such pain is defined as stemming from the thought processes or emotional state, and specifically excludes an organic cause. However, whether pain can appear solely as a result of a psychological state and without a physical stimulus is controversial, as described in the conflicting IASP definitions of “AFP” and “pain” - respectively, “pain of psychological origin...” and “an unpleasant sensory and emotional experience...”.

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Atypical facial pain - an uncertain diagnosis?

AFP is a condition that has, in general, been poorly identified by medical and dental practitioners. Unfortunately, there is a paucity of quality published research on AFP, probably related to the difficulty in defining the condition. Indeed, much of the published work of AFP in journals (Cooper et al., 1991; Melzack et al., 1986; Harness and Rome, 1989) and textbooks of (orofacial) pain (Loeser, 1987; Mahan and Alling, 1991; Graff-Radford, 1995; American Academy of Orofacial Pain, 1996) is anecdotal and relies on the personal, clinical experiences of the author(s) - such as the description of AFP by Schwartz and Chayes (1968) - “Atypical facial pain is usually deep-seated and very poorly localised. Initially, it is periodic but in time it becomes continuous. Many of patients are emotionally labile females with personality defects.” Moreover, for other texts specialising in orofacial pain, AFP is neither classified nor mentioned (Gelb, 1985, 1994; Cailliet, 1992).

Data from study 1 (chapter 1) suggests that AFP is a frequently diagnosed condition in chronic orofacial pain patients, but is probably the most difficult chronic orofacial pain condition to diagnose as it is associated with vague signs and symptoms. In this condition, many wide-ranging symptoms may be reported by the patient, yet few clinical signs are obvious for the practitioner. In particular, a symptom such as pain, is by nature, subjective, and relies on sensory and affective descriptors from the MPQ. Complicating the diagnosis for the practitioner, pain is subjective from the perspective of the patient, and perhaps the description of pain is profoundly influenced by psychosocial and environmental factors. In a
similar fashion, claimed pain intensity scores by the patient may contradict the clinical observations of the practitioner.

Mahan et al., (1991) have described a number of clinical features they consider pertinent to patients with AFP; first, the patient’s description of his / her pain is usually extensive, and common treatment modalities such as analgesics or surgery fail to abolish or reduce the pain; second, widespread pain sites are frequently described that cannot be explained by anatomical structures or neural pathways; third, there is often a long history of pain, and the patient response to the initial cause (often innocuous) is far greater than can be reasonably expected. AFP has probably been used by many practitioners as a convenient diagnosis when there is a long and complex pain history, in addition to no detectable pathology.

Psychosocial factors and the "pain-prone" patient

Notwithstanding the ‘apparent’ absence of pathology, published work suggests the importance of psychosocial variables in diagnosis, treatment and investigation of AFP. Mahan et al., (1991) have suggested that the facial features and the muscles of facial expression have important contributions as to how a patient perceives him / herself - that facial expression is often the main form of communication for emotional responses such as sadness, grief, anger and joy. Craig et al., (1992) have said that hypochondriacal patients often pay particular attention to their teeth and facial features, and will often seek extensive treatment to correct a minor problem; clinically, the patient presents as a “pain laureate”. Gordon et al., (1983) have reported that anxiety and depression are more evident in facial pain patients compared with other pain patients, and "abnormal illness behaviour" may
predate pain onset. Other, more serious delusional episodes may result in self-mutilation (or Münchausen’s syndrome by proxy) resulting in pain (Scully, Everson and Porter, 1995). Operant conditioning may exist between patient and doctor, such as the continual advice on pain relief or cure for intractable chronic pain, and secondary emotional gain may be present between patient and caregiver, the continuance of pain to obtain support, sympathy and control (Mahan et al., 1991). They also report that AFP has the highest rate of compensation claims for any chronic orofacial pain condition and until a claim is settled, there is little likelihood of improvement.

Analysis of socio-economic data in a "pain-prone" group found that 16% of patients had been subject to past physical abuse, and 63% reported a family member or friend to have a chronic physical handicap (Goss, Speculand and Hallet, 1985). AFP patients compared with TMD patients have shown a significantly higher anamnestic index (subject’s perception of pain) and a higher index of “disease conviction” (Gerke, Richards and Goss, 1992) - “disease conviction” defined by the investigators as being comprised of symptom preoccupation, an affirmation that physical disease is present, and rejection of the clinician’s reassurance. TMD patients have also been described as “distressed individuals who are beleaguered by physical illnesses” (Marbach, Lennon and Dohrenwend, 1988).

2.2 Aims
Based on the results of study 1, the most prevalent condition diagnosed was AFP. However, this diagnostic term generates considerable controversy. The primary aim of this study was to analyse psychosocial data from a group of patients diagnosed with AFP. The secondary aim was to illustrate the variability of AFP, and to discuss diagnostic and treatment parameters of this condition through representative patient case studies.

2.3 Patients and methods

The cohort of subjects was patients diagnosed with AFP from study 1. Data collected from the pain questionnaire included a number of variables - gender; age; MPQ; VAS; temporal quality of pain; duration of pain; word description of severity of pain (“mild / medium / severe”); aetiology of pain (“dental treatment / idiopathic / trauma / surgery / fall / motor vehicle accident / illness”); frequency of other painful body sites; frequency of ‘stress’ with pain; marital status (“married / widowed / divorced / separated / single”); the effect of pain on social life and employment (“significant effect / no effect”); number of practitioners from different disciplines consulted for pain (including medical and dental specialists, and alternative health practitioners); expectation of “pain being cured” (“certain / likely / uncertain / unlikely / impossible”); percentage of “pain reduction acceptable for the patient to live with”.

Three representative case studies are presented to illustrate the complexity of AFP with regard to diagnosis and treatment: a patient with AFP with significant psychological problems, a patient with AFP-TMD, and a patient with AFP-TMD who has responded to treatment.
2.4 Results
There were 34 females and 16 males (gender difference: P < 0.0001, chi-squared test, study 1 results) with an age ranging from 24-82 years (mean = 56, S.D. 15). Data for the AFP diagnoses (AFP or AFP-TMD) and mean values for MPQ, VAS and temporal pain quality have been previously reported in study 1. Individual subject pain scores are plotted separately - those diagnosed with AFP [PRI(T) and VAS], and those diagnosed with AFP-TMD [PRI(T) and VAS] (Figure 2.1). The duration of pain ranged from three months to 34 years (mean = 7.6, S.D. 9.4) and were thus clearly non-normally distributed. The severity of pain (n = 36) was reported to be “medium” in 10 subjects and “severe” in 26 subjects. The aetiology of pain was attributed to dental treatment (n = 9), idiopathic onset (n = 14), trauma (n = 2), surgery (n = 1), fall (n = 5), motor vehicle accident (n = 3) and illness (n = 4) (Figure 2.2). Sixty-three percent of subjects claimed to have other painful body sites. ‘Stress’ concurrent with pain was reported to be present in 76% of subjects. The marital status of the group showed 18 were married, 10 widowed, eight divorced and four separated. Pain had a significant effect on the social life and / or employment on 90% of subjects. The number of practitioners consulted for pain ranged from two to thirteen (mean = 6, S.D. 4). Subjects’ (n = 37) expectation of the “pain being cured” was certain (n = 6), likely (n = 10), uncertain (n = 12), unlikely (n = 7) and impossible (n = 2) (Figure 2.3). The percentage of pain reduction acceptable for the patient to live with varied from 1-100% improvement (mean = 66.2, S.D. 34.9).

Figure 2.1
Distribution of VAS among the AFP (n =18) and the AFP-TMD (n = 19) groups.
Figure 2.2
Distribution of aetiology of pain as reported by subjects.
Figure 2.3
Distribution of subjects’ expectations of “pain being cured” from treatment.
A 47 year old female had a 20 year history of pain involving bilateral aspects of the face that was centred in the left and right temporomandibular joints. Further areas of chronic pain were reported to include shoulders, back and knees. The pain increased in severity from weather changes, cold weather and eating. Sometimes, "only a pain injection" would decrease the pain for a short period. The patient was divorced and claimed the onset of pain followed a "broken jaw suffered on my honeymoon". There had been five confirmed operations to the temporomandibular joints, and a reported (but unconfirmed) 37 other operations, mainly to the breasts and genital region. The pain was rated as 6/10 (VAS) and sensory pain descriptors included “throbbing, stabbing, searing and aching” qualities. The pain was “continuous and severe” and affective descriptors listed were “frightful, exhausting and agonising” qualities. In contradiction, the patient claimed she was “cheerful most of the time, definitely relaxed, not tense and never gets frightened”. No previous psychiatric assessment was reported by the patient, and she declined further treatment when advised that Pain Centre psychiatric or psychological assessments were necessary.

**Commentary:** While the patient declined an opportunity to explore possible psychological aspects of her pain, examination of her pain report and responses on interview suggests that she is reacting to her pain in excessively negative and unhelpful ways. At the same time she is taking a passive approach to its management, expecting the practitioner to fix the problem and taking no responsibility herself - in fact denying any role she had to play. Her approach is suggestive of a poor outcome, greater distress and disability, and continued high use of health care services. The patient claimed "constant, severe and agonising pain" at her initial consultation, yet appeared in no obvious distress. Indeed, there were frequent episodes of laughter from the patient and she stated she was "proud" of her history whereby surgery had
failed to "take away the pain". While the numerous surgical procedures may have caused neuropathic pain, the patient steadfastly refused to undergo patient-blinded placebo (saline) / lignocaine infusions for neuropathic pain assessment, and psychological / psychiatric evaluation. No evidence of a secondary TMD was evident.

**Case Study 2 AFP-TMD**

A 68 year old female, married and living with her husband, had a 34 year history of orofacial pain which had "spread to the neck, abdomen and back". The pain started after dental treatment and had severely affected her occupation as a social worker. The pain was rated as “continuous and severe” and was scored as “10+++” (patient’s writing) on the VAS (10 = “worst pain imaginable”). Many pain descriptors were listed (“thробbing, shooting, pricking, cutting, cramping, scalding, stinging, heavy, exhausting, suffocating, frightful, vicious, blinding, intense, penetrating, tight, numb and torturing”) and at least 12 different medical / dental / alternative health disciplines had been consulted for unequivocal pain relief. The patient was “certain that the pain would be cured” and preferred a 100% pain reduction as being acceptable to live with, despite the long pain history. Her expectation was “that someone out there has the knowledge to fix me”. The patient exhibited a secondary TMD and was advised that, although some pain reduction would be expected with TMD treatment, long term pain management was necessary for a realistic outcome. Later correspondence from the patient to the pain centre advised that she had "found a naturopath skilled in dental matters and who would rid her body of dental poisons that caused the pain".

*Commentary:* Case 2 shows a patient with multiple sensory and affective pain descriptors indicating psychogenic and pathophysiological variables, and an unrealistic expectation of
pain relief / pain management. She “did not want to talk about the pain”, but instead wanted to expound on her past merits and problems encountered as a social worker. A primary diagnosis of AFP was given following further consultation with the clinical psychologist. However, the patient also exhibited multiple signs and symptoms of TMD - facial muscle tension and spasm, bruxism, restricted oral opening, temporomandibular joint pain, frequent headaches and neckache.

**Case Study 3 AFP-TMD**

A 55 year old female, divorced and engaged in voluntary church work, had a 6 year history of orofacial pain. The cause of the pain was unknown although there was a history of a fractured skull and jaw. The pain was “periodic” and rated “10/10” on the VAS. Many pain descriptors were listed - “quivering, flashing, stabbing, sharp, pressing, wrenching, burning, tingling, aching, heavy, rasping, exhausting, sickening, terrifying, vicious, wretched, miserable, radiating, tearing, freezing and torturing” qualities. The patient also exhibited signs and symptoms indicative of an accompanying TMD: jaw joint pain and clicking, neckache, headaches, sore tongue, dizziness, restricted oral opening, facial muscle tension, numbness in the face and sinusitis-like symptoms. The patient was edentulous and wore ill-fitting upper and lower dentures.

**Commentary:** Case 3 shows a patient with multiple sensory and affective pain descriptors suggesting the patient was finding the pain quite distressing. However, in contrast to case study 1, this woman developed a more balanced lifestyle and kept quite active, apart from when the pain was at its worst. She was not unrealistic in her expectations for treatment and was able to share the responsibility for the management of her pain, as evidenced by her
good compliance with the treatment and acceptance of reassurance. Treatment included a tricyclic antidepressant (doxepin) and construction of new dentures. She reported a 90% reduction in pain when later reviewed. There were occasional breakthrough episodes of pain for which simple reassurance was effective.

2.5 Discussion
Results from this study show the significantly higher female occurrence of AFP; this has been discussed in study 1. The mean age for AFP is similar to the results from study 1 for the larger orofacial pain group, i.e. no definitive conclusion can be reached as to the predilection of menopausal / post-menopausal females to have AFP, and that further studies are needed particularly in the area of hormonal factors.

The aetiology of AFP was directly attributable to a physical stimulus (nociception) in 63% of subjects (dental treatment, trauma, fall, surgery, illness). This certainly provides evidence of underlying but undetected pathophysiology in AFP. Pain report and presentation appears either magnified or minimised by psychological factors rather than caused by them, as illustrated in the case studies. Psychological and environmental factors (beliefs, emotional state, socio-economic, cultural and educational variables) may play a major role in a substantial number of patients diagnosed with AFP, as with chronic pain generally. However, the extent to which psychological and environmental factors influence chronic pain from published data is controversial (Zborowski, 1952; Engel, 1959; Zola, 1966; Kuhn et al., 1979; Blumer et al., 1981; Flannery et al., 1981; Gordon et al., 1983; Weisenberg et al., 1989; Greenwald, 1991; Calvillo and Flaskerud, 1993).
The majority of patients (62.5%) claimed to have “other painful body sites” (10/20 subjects with AFP and 15/20 subjects with AFP-TMD, P < 0.01, chi-squared test). "Pain-prone” patients have been shown to report pain that is present in multiple locations. The frequency of “other painful body sites” appears variable: 100% of patients with facial arthromyalgia or AFP had multiple pain sites (Feinmann, 1993); 65.1% of TMD patients (McGregor, Butt et al., 1996); and for pain sites of non-orofacial origin, 65.8% for females and 47.7% for males (James et al., 1991) and 37.9% of subjects (Krause, Tait and Margolis, 1989).

Other data supporting the concept that AFP patients are “pain prone” include continuous pain (90% of patients), and pain with a sudden non-traumatic onset (Blumer et al., 1981; Goss et al., 1985). Moreover, the rejection of the clinician’s advice as described in case studies 1 and 2 strengthen the view that there are at least some “pain-prone” AFP patients.

A large number of patients (76%) reported ‘stress’ concurrent with pain. The intimate association of pain with stress has been shown by McGrath (1994). Much discussion has been centred on the relationship of stress to TMD (Lundeen, George and Sturdevant, 1988; Marbach, et al., 1988; Schleifer et al., 1990), and the findings of Rudy (1990) are noteworthy - pain intensity ratings doubled when stress was present.

As expected with any chronic condition, there were multiple practitioner consultations. Probable causes would be the ongoing expectation of cure, and the patients’ acceptable level of pain “to live with”. Marbach and Lipton (1978) found several patient background factors as reasons of continued practitioner visitation - patients ‘‘ were relatively unknowledgeable about health matters, generally demanding of doctors, and sceptical of
doctors’ general abilities, usually shopping around for health care providers”. Pain had a significant effect on the social life and/or employment on 90% of subjects. Fordyce, Lansky et al., (1984) and others (Blumer et al., 1981) have previously shown a strong and positive correlation between pain severity and impairment of activities. Furthermore, Suvinen, Reade et al., (1997) have shown in TMD patients that cultural variables may influence the extent of pain on work activities.

The generally accepted defining factor for AFP has been the lack of pathophysiological mechanisms, thus precluding an organic component to AFP. However, this study showed that TMD was identified in 50% of AFP patients. TMD is an organic disorder with a complex of signs and symptoms involving the oral cavity, face, head and neck that has pain as its most frequent symptom. Pain arising from TMD is predominantly due to bruxism (jaw clenching and tooth grinding). 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. Although bruxism may be a pain-coping mechanism for the primary disorder (AFP), a secondary pain complaint is established. Similarly, it has been suggested that a potential positive feedback loop exists in the orofacial region - the facial expression of pain (e.g. grimacing) results in accentuated muscle contraction (involving the muscles of facial expression) which leads to greater pain intensity (Fiske et al., 1991). The frequency of signs and symptoms of TMD in this study (Table 2.1) can be compared to data compiled by others (Bezuur, Hansson and Wilkinson, 1989), who found in their study, patients with facial pain (86%), limited oral opening (49%), temporomandibular joint clicking (48%) and painful temporomandibular joint (45%).
2.5.1 AFP case studies - diagnostic and treatment guidelines

Several important variables may influence the diagnosis and treatment of AFP patients. First, it is likely the patient and doctor do not share the same definitions of 'pain', 'hurt', and 'suffering'. The difficulties of accurately conveying information and impressions are readily apparent in the variability of 'clinical pain intensity' as measured by the VAS, where a patient rates pain intensity at 10/10 during consultation and yet appears in no distress. Second, the patient's response to a seemingly innocuous physical stimulus may appear far greater than might be reasonably expected by the practitioner. Widespread pain areas or pain that 'migrates' in the orofacial region can be reported, yet cannot be explained by anatomical structures or traditional "hard-wired" neural pathways. Feelings of frustration can be experienced by the medical practitioner when common treatment modalities such as surgery fail to abolish or reduce the pain. This treatment rationale is based on the outdated Cartesian model of pain - surgical removal of the peripheral painful area is hoped to remove the pain.

A UK study of iatrogenic factors of chronic pain syndromes showed patients’ expectations of cure persist despite the repeated failure of treatment (including surgery) to alleviate pain (Pither and Nicholas, 1991). In detriment to the patient, multiple surgical procedures to a pain site may result in the development of a painful neuropathy. Complicating the picture of neuropathic pain is associated sympathetic hyperfunction, allodynia, hyperalgesia and hyperpathia. Furthermore, there is now good evidence that neuropathic pain of the oral cavity exists (as a condition previously termed AO), and this condition is often precipitated by dental treatment (Marbach 1993a, 1993b; Epstein et al., 1994). AO is poorly understood and possibly misdiagnosed as AFP (Fishbain, Trescott et al., 1993). The
possibility that AFP may originate as another form of intraoral neuropathy, with or without
dental treatment (or other physical causes) as a trigger, is worth considering based on
patients' responses to the MPQ. In particular, the sensory descriptors of pain frequently
listed by patients are very similar to those used to describe other chronic orofacial pain
conditions with a pathophysiological basis (such as AO). MPQ descriptors are useful but
not diagnostic; however, it at least raises the possibility that AFP patients may have pain
based on similar biochemical mechanisms from undetected pathophysiology. Considering
that underlying pathophysiology may be present in AFP patients, several guidelines are
suggested in the examination and diagnosis for patients: the need to correctly categorise the
condition (Dubner, 1990); a good knowledge of orofacial pathology; a thorough
understanding of pain pathophysiology (Casey, 1990); and a multidisciplinary approach to
diagnosis and treatment, typically involving assessments by an anaesthetist (pain specialist),
physiotherapist, clinical psychologist / psychiatrist and dental surgeon.

There is a vast range of conditions in orofacial pathology where pain is a frequent symptom.
For example, such pathology (with pain) to consider in the differential diagnosis would
include: AO that is characterised by a constant pain at a tooth site and that can spread to
adjacent mucosal tissues; TN that has short, sharp, excruciating pain; burning mouth
syndrome with a constant, burning quality; impacted third molar teeth with periodic pain;
temporomandibular joint pathology (displaced joint disc, rheumatoid / osteoarthritis); other
conditions with a possible referral pattern to the orofacial region such as temporal arteritis,
carotidynia, maxillary sinusitis, salivary gland pathology, neurological disorders and
headache syndromes (tension, migraine, etc.). Accordingly, multiple diagnostic procedures
to screen for pathology would include radiographs, computerised tomography and magnetic resonance imaging, and blood screens. In addition, sequential analgetic blockade should be undertaken to determine the location of peripheral pain sites - topical anaesthetic application, followed by local anaesthetic infiltration, then regional blocks, and specific tests such as stellate block, cervical facet joint blocks, and placebo-controlled, patient-blinded infusions such as saline / lignocaine and saline / phentolamine infusions for assessing neuropathic pain and sympathetically maintained pain (SMP), respectively.

An understanding of pain pathophysiology, particularly with regard to neuropathic pain is probably crucial, as often this form of pain is little understood among general practitioners. The difficulty in diagnosing such pain states for a general practitioner is that no pathology is detected on routine clinical and radiographic examination. Thus, this may lead the practitioner to the controversial “pain of psychogenic origin” - a diagnosis more often than not based on an absence of demonstrable pathophysiology, rather than positive evidence of psychological factors playing a causal role as well. Diagnosis by exclusion is clearly to be avoided. It is important, therefore, that multidisciplinary pain assessments are carried out by experienced pain specialists. Assessment of psychological factors in patients presenting with complaints like AFP requires considerable skill and experience. 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 there is scope for previously undetected pathophysiology to exist, as exemplified in this study where a substantial number of patients had TMD that had been previously overlooked.

Results of analysing the cohort of patients in this study generally showed that patients had uncertainty about future pain relief, yet expected a substantial degree of pain reduction from the attending doctor / practitioner. Indeed, unequivocal pain relief was demanded by some patients, despite many years of suffering and failed treatments. Unfortunately, inordinate pressures can be placed on medical and dental practitioners by chronic orofacial pain patients regarding analgesic prescriptions. Initial treatment and long term management from a specialist pain centre, as evidenced from the case studies, must utilise a broad range of measures individually tailored to the patient:

(i) rationalisation of drug regimens to reduce and eliminate, where possible, opioids, sedatives and other drugs of dependence and initiation of long term low dose tricyclic antidepressants, adjunct medications such as anticonvulsants (carbamazepine, sodium valproate) and membrane stabilisers (mexiletine);

(ii) initiation of physical therapy to jaw, neck and other musculature;
(iii) institution of specialist psychological / psychiatric treatment focusing 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 person's life; and

(iv) dental splints and occlusal rehabilitation where appropriate, if an associated TMD is present.

2.6 Conclusion

A diagnosis of AFP is usually based on the exclusion of known pathology that causes pain in the orofacial region. In this study 40 chronic orofacial pain patients were diagnosed with this condition based on multidisciplinary pain assessments. However, an analysis of these patients showed 50% to exhibit a local pathological component (TMD) that contributed to pain intensity. Where TMD is associated with the primary diagnosis of AFP, there is a need for caution in employing the traditional AFP diagnosis. Other recent studies indicate that intraoral neuropathic pain (AO) may be mistakenly diagnosed as AFP. In all probability, AFP would cover a "mixed bag" of conditions ranging from undetected pathology to pain that is hallucinatory in origin. Thus, the practitioner is left to speculate about the basis of the pain.

Traditionally, AFP is characterised by continuous and severe pain. This study, consistent with the findings of the few available studies of this condition, found a high incidence among females in the postmenopausal age group, with the majority of AFP patients living alone. The majority of patients were divorced, separated, widowed or single. There was often an
unrealistic expectation of pain relief, based on the pain history. Some data of AFP patients were representative of the description of the “pain-prone patient”. These data strengthen the current AFP definition as “pain of psychological origin”. On the other hand, other data were highly indicative of a physiological component involved with AFP: MPQ sensory pain descriptors were ticked by every subject; there were a significant number of patients with an associated TMD; the significant gender difference and age group from possible underlying influences of hormonal factors.

It is highly probable that all patients diagnosed with AFP have underlying pathophysiology that is difficult to detect and poorly understood. However, psychological variables and environmental factors may play a substantial or overwhelming role during patient-practitioner consultation and thus would account for the traditional diagnosis of AFP based on exclusion of pathology. Treatment for AFP necessitates the multidisciplinary approach to pain management utilising drug rationalisation, psychological / psychiatric intervention, and for patients with an associated TMD, additional physical therapy and dental rehabilitation. A number of factors warrant the need for further studies into AFP - the condition is frequently seen among orofacial pain patients, the current IASP definitions are inadequate and controversial, and there is a paucity of evidence-based data on which to draw definitive criteria for diagnosis, and guidelines for treatment.
### TABLE 2.1

Frequency of TMD Signs and Symptoms in AFP-TMD Patients (n = 14)

<table>
<thead>
<tr>
<th>TMD sign / symptom</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>facial / jaw pain</td>
<td>86</td>
</tr>
<tr>
<td>Condition</td>
<td>Score</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>neck pain</td>
<td>79</td>
</tr>
<tr>
<td>headaches / earaches</td>
<td>79</td>
</tr>
<tr>
<td>temporomandibular joint pain</td>
<td>79</td>
</tr>
<tr>
<td>facial / masticatory muscle tension</td>
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</tr>
<tr>
<td>bruxism</td>
<td>64</td>
</tr>
<tr>
<td>clicking of temporomandibular joint</td>
<td>50</td>
</tr>
<tr>
<td>difficulty in chewing</td>
<td>43</td>
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<tr>
<td>restricted oral opening</td>
<td>43</td>
</tr>
<tr>
<td>dizziness</td>
<td>43</td>
</tr>
<tr>
<td>teeth chipping/wearing down</td>
<td>29</td>
</tr>
<tr>
<td>unpleasant taste</td>
<td>29</td>
</tr>
<tr>
<td>tingling sensation in face</td>
<td>29</td>
</tr>
<tr>
<td>numbness in face</td>
<td>29</td>
</tr>
<tr>
<td>locking of jaw</td>
<td>29</td>
</tr>
<tr>
<td>tinnitus</td>
<td>21</td>
</tr>
<tr>
<td>difficulty in breathing through nose</td>
<td>21</td>
</tr>
</tbody>
</table>
CHAPTER 3

STUDY 3: AN EVALUATION OF PHARMACOLOGICAL PROCEDURES FOR THE DIAGNOSIS AND TREATMENT OF ATYPICAL ODONTALGIA

Published in part as:

3.1 Introduction

AO is a chronic pain condition that is poorly understood, inconsistently presented in the literature, and with a paucity of information regarding diagnostic and treatment / management procedures. AO was first described as a painful and unusual condition that occurs in the dento-alveolar structures and oral mucosa (Rees and Harris, 1979). The pain is moderate to severe in intensity and has a pattern of referral that can cross the midline of the mandible and maxilla and may involve the face. The location of pain may occur in single or multiple sites, and can be particularly difficult to diagnose by dental and medical practitioners. It has been described as "phantom tooth pain" due to insufficient data in providing a physiological explanation and its similarities to phantom limb pain (Marbach, 1993a, 1993b; Houghton, Nicholls *et al*., 1994). The differential diagnosis of AO has included cracked tooth syndrome, AFP, migrainous neuralgia and sinusitis. The condition occurs infrequently, with the dental surgeon(s) (and specialists) often confident in alleviating the problem by operative means, only to find that the various (and often numerous) procedures undertaken fail to abolish the pain (Kreisberg, 1982; Campbell, Parks and
Dodds, 1990). Perhaps the greatest difficulty for the general practitioner and specialist is the absence of clinical and radiographic evidence to establish a diagnosis pertaining to organic pathology, thereby suggesting a psychogenic basis to the condition. The IASP has defined AO as a "severe throbbing pain in the tooth without major pathology" (Merskey, 1986; Merskey et al., 1994).

While other chronic orofacial pain conditions such as TMD have had extensive documentation, relatively few studies investigating AO have been published. Complicating our understanding of AO has been the limited number of patients analysed; [Rees et al., 1979 (n = 44); Marbach, 1978 ("phantom tooth pain", n = 25); Brooke, 1980 (n = 22); Kreisberg, 1982 (n = 2); Pöllman, 1993 (n = 44)]. However, most of these published data are epidemiological and there are little data available for clinicians with respect to diagnostic tests and treatment modalities. The aetiology of AO has been linked with vascular changes to local tissues (Rees et al., 1979) and there is evidence that a psychogenic component to the condition is present in a large number of patients (Rees et al., 1979; Graff-Radford and Solberg, 1993). The accepted treatment for patients has primarily included long term antidepressant therapy, although not all sufferers respond with a reduction in pain. Thermographic studies (Gratt, Sickles et al., 1989; Graff-Radford, Ketelaer et al., 1995) and other clinical trials (Epstein et al., 1994) suggest that AO is a neuropathic pain condition of the oral cavity; further endorsed by the compelling arguments of Marbach (1993a, 1993b), an experienced clinician in the field of AO.
A clinical characteristic of AO has been the variable pain reduction response from local anaesthetic blocks - complete, partial or no relief in a limited study of 13 patients (Bates and Stewart, 1991). Adding to the confusion surrounding this variable pain reduction response have been anecdotal reports with opposing views on pain relief from somatosensory blockade (Rees et al., 1979; Graff-Radford and Solberg, 1992). An investigation of this potentially important diagnostic characteristic was thus warranted, and for this study, the first stage of sequential analgetic blockade was assessed. This consisted of an application of a topical anaesthetic cream (EMLA) to the peripheral pain sites. EMLA cream 5% (Astra Pharmaceuticals Pty Ltd, NSW, Australia), a relatively new topical anaesthetic agent, is a eutectic mixture of local anaesthetic bases (lignocaine and prilocaine). The agent is used for medical applications (Juhlin, Evers and Broberg, 1980; Cooper, Gerrish et al., 1987; Goodacre, Sanders et al., 1988) and has been shown to have rapid oral mucosal absorption and to penetrate deeply into the oral tissues (Vickers and Punnia-Moorthy, 1992, 1993).

Studies using thermography (Gratt et al., 1989; Graff-Radford et al., 1995) and stellate ganglion block (Lynch and Elgeneidy, 1996) have implicated SMP as occupying a role in AO. Stellate ganglion block has been used as a diagnostic test for SMP in head, neck and upper limb (Bonica, 1990). 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 inability to conduct blinded, placebo-controlled injections (Walker and Cousins, 1997). More recently, 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 success of subsequent sympathetic blocks (Arnér, 1991; Raja, Treede et al., 1991). In addition, the phentolamine test has the advantages of being less invasive and less painful, and blinded, placebo-controlled infusions can be administered.

Early evidence-based treatment of AO employed long term tricyclic antidepressant medication with adjunct psychological interventions (Rees et al., 1979). More recently, Epstein et al. (1994) assessed the efficacy of topical applications of capsaicin in treating oral neuropathic pain (AO), with promising results. Capsaicin (8-methyl-N-vanillyl-6-noneamide), commonly known as cayenne pepper, is derived from capsicum fruit. The agent is widely used in pain research (Dubner, 1991a; Dray, 1992; Maggi, 1992; Craft and Porreca, 1992). Its prime role for medical applications has been for the treatment of dermal lesions from post-herpetic neuralgia in humans (Bernstein, Korman et al., 1989; Stanberry, Bourne et al., 1992). The substance has both algesic and analgesic properties, and topical application reduces inflammation by depleting potent algogens (pain-producing agents) such as bradykinin and histamine (Crimi, Polosa et al., 1992; Cordell and Araujo, 1993). Capsaicin causes a reduction in unmyelinated capsaicin-sensitive [substance P, calcitonin gene-related peptide (CGRP)] fibres (Gyorfí, Fazekas and Rosivall, 1992; Zhao, Yang et al., 1992), which are restricted to afferent neurons (C and Aδfibres) (Bevan and Szolcsányi, 1990; Lynn, Ye and Cotsell, 1992).

3.2 Aims
Considering the paucity of data for AO, there were a number of objectives for this study.

1. To analyse patient self-report data based from a pain questionnaire (i.e. similar to study 1):
   a) to obtain more information on the epidemiology of the condition pertaining to gender, age and socio-economic variables;
   b) to analyse possible aetiological factors as claimed by the patients;
   c) to analyse data from pain variables (particularly pain descriptors) that may assist in defining the type of pain that is present.

2. To evaluate a number of pharmacological interventions to aid in the diagnosis and management of AO:
   a) to assess the effect of topical applications of EMLA applied to intraoral pain sites for any pain reduction, suggesting an area of hyperalgesia;
   b) to carry out controlled, blinded saline / phentolamine infusions for measuring any sympathetic contribution to AO;
   c) to assess topical applications of capsaicin for diagnostic purposes in evaluating whether AO has a neuropathic pain component, and its possible therapeutic potential in treating AO.

3.3 Patients and methods
Patients were recruited from the investigator’s institution and included the patient group diagnosed with AO in study 1.

3.3.1 Pain questionnaire and multidisciplinary pain centre assessment

Subjects completed a comprehensive pain questionnaire that included demographic and socio-economic factors, pain variables (VAS, MPQ and temporal pain qualities), and a section specifically for evaluating TMD. Patients were diagnosed by the pain centre oral surgeon (the investigator) in collaboration with other pain centre personnel (anaesthetist / pain specialist, psychologist, psychiatrist and physiotherapist). A diagnosis of AO was based on general criteria previously reported (Marbach, 1993b; Bates and Stewart, 1991).

3.3.2 Topical application of EMLA

EMLA cream 5%, on a cotton bud, was liberally applied to the mucosal / gingival tissues where the patient complained of intraoral pain. The test site was wiped free of excess saliva prior to the placement of EMLA, with the agent well localised for a standardised five minute application time. Patients were asked to indicate the degree of reduction in pain intensity (%) compared with baseline pain levels (before EMLA application). Where patients had multiple sites of pain, EMLA was placed on the original site of pain only.

3.3.3 Sympathetic blockade
Twelve patients were randomly selected throughout the study to undergo patient-blinded, placebo-controlled sympathetic blockade by phentolamine infusion. Patients were monitored with electrocardiograph, pulse oximetry and non-invasive blood pressure measurements. Initially, 500 mL of intravenous normal saline (0.9%) was administered to limit potential hypotension from phentolamine. VAS scores were recorded at baseline and at five minute intervals. The trial involved a placebo infusion of saline over 10 minutes followed by phentolamine 15 mg over 10 minutes. If no analgesic response was reported by the patient and cardiovascular side effects were minimal (tachycardia and hypotension), further 5 mg bolus doses of phentolamine were administered until a response was seen (pain relief or moderate side effects).

3.3.4 Treatment efficacy of topical capsaicin

Patients were instructed to complete a diagnostic trial of capsaicin 0.025% cream (Capsig, Sigma Co., Clayton, Australia) applied topically for four weeks. The procedure involved the application of a proprietary topical anaesthetic mouthwash (benzocaine 15%, amethocaine 1.7%) for three minutes, prior to capsaicin placement, in order to achieve a pain-free application of the agent. Capsaicin was applied for three minutes, morning and evening, for four weeks. Patients were reviewed and reported any change in pain intensity (VAS) from the four week trial. Long term pain relief was recorded at least three months after the trial was completed to minimise any pain reduction by placebo effect.

Statistical analyses
Chi-squared tests were used to assess any significant change in pain reduction from EMLA application, phentolamine infusion and the four week trial of capsaicin. Student's t test was used to assess any significant change in pain ratings from the four week trial of capsaicin compared with pain ratings at long term review.

3.4 Results

Over a three year period, 50 patients (34 females and 16 males), with an age range from 21-82 years (mean = 51 years, S.D. 15), were diagnosed with AO. A summary of individual patient data is shown in appendices 3-6. The major source of referrals were from dental practitioners (n = 37) and 13 patients were referred from medical practitioners. Demographic data showed 33 subjects born in Australia, 12 in Europe, three in Asia and two in Africa. The ethnicity of the group was 48 caucasians and two orientals. Results of the patients who completed the marital status section of the questionnaire (n = 49) showed the majority were married (n = 33), with the remainder being separated / divorced (n = 6), single (n = 6) or widowed (n = 4). Forty patients lived with their families, two patients with friends and eight patients lived alone. The listed occupational status included employment (n = 22), domestic duties (n = 16), pension (n = 10) and unemployed (n = 2). When asked whether the pain had significantly affected their work performance or social life (n = 46), 29 patients reported a significant effect and 17 patients claimed little or no effect. The majority of patients were non-smokers (n = 38/50) and 10/50 consumed alcohol on a daily basis.
The duration of pain experienced in the group ranged from three months to 32 years (mean = 4.9 years, S.D. 6.7) and was not normally distributed. Aetiology of pain (n = 50) was reported to be directly attributable to dental treatment (n = 37), dental infection (n = 3), dental trauma (n = 1) and idiopathic onset (n = 9). Results of completing a three word pain intensity scale (“mild, medium or severe”) showed the majority of patients reported the pain as “severe” (n = 23), 16 patients indicated “medium” levels of pain, and five patients indicated “mild” pain. A 10 cm VAS completed by patients (n = 45), showed a range of pain scores from 3-10 (mean = 7, S.D. 2), with five patients claiming the pain as “worst pain imaginable” (10 cm). On a three point scale assessing the temporal quality of pain (constant, periodic or transient), 40 patients indicated “constant” pain and 10 patients reported “periodic” pain.

Patients listed that the number of consulting practitioners (medical specialists, dental specialists and other health practitioners), prior to referral and specifically for orofacial pain, ranged in number from 1-17 (mean = 5, S.D. 3). Sixty per cent of respondents (n = 43) indicated that cure of their condition was uncertain (n = 17), unlikely (n = 8) or impossible (n = 1). The survey showed that 66% of patients reported concurrent “stress” with the pain (27/41). Causation of stress was predominantly due to family, financial, work, bereavement, health or pain-related factors.

Clinical examination of patients showed that 15 patients were suffering from AO solely, while 35 patients had AO with an accompanying TMD (AO-TMD). The large majority of
patients with an associated TMD claimed that the TMD signs and symptoms occurred after the onset of intraoral pain from AO.

Results of the five minute diagnostic trial of EMLA to the area of intraoral pain (n = 38) demonstrated a significant reduction in pain ranging from 0-100% (mean = 60, S.D. 29; P < 0.0001) (Figure 3.1). Results of the phentolamine infusion to assess a possible sympathetic component to the pain (n = 12) showed a significant reduction in pain ranging from 0-80% (mean = 31, S.D. 27; P < 0.0001), with no noticeable pain reduction from the saline infusions. Results of the 4 week trial of 0.025% capsaicin cream (n = 30) showed significant pain reduction with 19 subjects responding positively with a reduction in pain ranging from 10-100% (mean = 58, S.D. 25; P < 0.0001) (Figure 3.2). The remaining 11 subjects claimed no benefit (nil pain reduction) from capsaicin. At long term follow up (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% (S.D. 34; P = 0.25).
Figure 3.1
Distribution of percentage pain reduction from pharmacotherapeutic diagnostic procedures. Pain reduction significant from EMLA application (mean reduction = 59, S.D. 29; \( P < 0.001 \)) and phentolamine infusion (mean reduction = 31, S.D. 27; \( P < 0.01 \)).
Distribution of percentage pain reduction from topical capsaicin treatment. Pain reduction significant from four week trial [mean=58%, S.D. 25; P < 0.0001; (n=30)], and maintained at long term review [mean = 50%, S.D. 34; (n=26)].
3.5 Discussion

3.5.1 General findings

Data analysis showed that AO did not have an increased prevalence in any particular group regarding ethnic origin or socio-economic status. The condition was seen to occur over the adult age range. The younger age group (children and teenagers) were not seen to suffer from the condition, unlike TMD which can be more frequent in this group. Pöllmann (1993) showed that there was a correlation between age and duration of "phantom sensations", however, no correlation was noted in this study. A greater percentage of patients was female, although no clear reason was evident, and similar gender differences have been identified in chronic orofacial pain (Gerschman et al., 1987). Results showed that most patients experienced “constant” and “severe” pain. Several patients claimed suicide (and one attempt) as an option to end their pain, underlying the serious nature of this condition.

A disturbing finding in this study was the mean pain duration, and the number of practitioners consulted prior to referral to the author’s institution. Many patients were relieved when informed of a diagnosis, despite subsequent advice on the lack of controlled studies offering definitive treatment. Indeed, several patients had complained that referring practitioners had alluded to the patient's "imaginary pain", based on the lack of abnormality from clinical and radiographic examinations. However, AO patients described many sensory MPQ descriptors (Table 3.1) indicative of underlying pathophysiology. Clearly, the lack of knowledge about AO, further complicated by little understanding of chronic pain pathophysiology, resulted in lengthy delays for pain centre referral from referring practitioners.
The investigator found that AO, far from being a rare condition, is relatively frequently encountered, as previously suggested (Campbell et al., 1990; Marbach et al., 1982), 25% of patients among a chronic orofacial pain population at the investigator's institution being diagnosed with AO (study 1). A study of 50 patients with "chronic idiopathic orofacial pain" (Allerbring and Haegerstam, 1993) showed that the pain has a remarkable similarity in aetiology when compared to pain in the current study (Table 3.2). Furthermore, a review of several case reports of "atypical facial pain" (Fishbain et al., 1993) and Münchausen's syndrome (Scully et al., 1995) suggests that a diagnosis of AO was probably indicated. A study of 3,126 adult subjects requiring oral examinations for prospective employment, showed that 44 patients reported "phantom tooth sensations" (Pöllmann, 1993), indicating that AO may be present in over 1% of the population. A higher figure of 3-6% of the population has been suggested by others (Marbach et al., 1982), based on a very limited study of endodontically-treated subjects, but with specific study parameters.

An interesting study by Nicolodi and coworkers (Nicolodi and Sicuteri, 1993) compared long term post-extraction pain in matched headache / control patients. Their results showed that no healthy control complained of "phantom tooth pain", but 20% of cluster headache subjects (n = 10/50 sufferers) and 14% of migraine headache subjects (n = 36/251 sufferers) reported symptoms, suggesting a predisposition of patients with certain forms of periodic pain to develop neuropathic pain following trauma. The possible connection of migraine and AO has been noted by others (Rees et al., 1979; Brooke, 1980; Schnurr and Brooke, 1992).
3.5.2 Aetiological factors

The aetiology of AO was attributed to dental treatment in a high proportion of patients (Table 3.2). The initiating factor from dental treatment varied from drilling dentine for a simple restoration, to root canal therapy and periodontal scaling. The highly innervated and vascular dental pulp, gingival and mucosal tissues are frequently subjected to repetitive stimuli (thermal, mechanical, chemical and biological) that can elicit pain. Thus, the potential for the development of neuropathic pain clearly exists. For possible central changes in ‘oral neuropathic pain’, tooth pulp deafferentation has been demonstrated to produce functional changes in the trigeminal nucleus (Hu, Dostrovsky et al., 1986). In addition, in the presence of nerve injury or chronic inflammation, sensitised C-polymodal nociceptors may be activated by noradrenaline (Sato and Perl, 1991; Sanjue and Jun, 1989). Therefore, noradrenaline or adrenaline in dental local anaesthetic cartridges may potentially exacerbate pain - this may be related to some patients in this study who reported a short episode of higher pain intensity following local anaesthetic injection during previous dental treatment(s).

This proposed hypothesis of a pharmacological aetiology of AO is supported by a number of factors: (i) the high incidence of dental procedures causing AO, as definitively reported by patients in this study; (ii) most (if not all) patients recollected the routine administration of local anaesthetic prior to the procedure; (iii) the routine use of vasoconstrictor (noradrenaline and / or adrenaline) contained in local anaesthetic cartridges, used in general dentistry in Australia (Astra Pharmaceuticals Pty. Ltd., personal communication); (iv) the added effect from the endogenous release of adrenaline caused by anxiety, prior to, and during the dental procedure (Taggart, Hedworth-Whitty et al., 1976). If further studies
support this concept, the use of local anaesthetics without adrenaline as a vasoconstrictor in AO patients may be advisable. Furthermore, in diagnosing AO, pain-free peripheral neural blockade assessment techniques such as EMLA, to quantitate its effect on baseline pain intensity, would be more accurate than perineural administration with local anaesthetic and vasoconstrictor.

In some patients, relatively innocuous dental procedures resulted in AO. This may suggest neurogenic / biochemical sensitisation with potential exacerbation by pharmacological agents as a causal factor in aetiology. The prospect of repetitive painful stimuli from dental procedures leading to central changes should also be considered, however a number of patients claimed no sustained or excessive pain from the dental procedure, yet developed AO. It is probable that the cause of AO is multifactorial, with several different contributing elements including pharmacological, biochemical / neural, environmental and genetic factors.

<table>
<thead>
<tr>
<th>Sensory descriptor</th>
<th>Frequency (%)</th>
</tr>
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</table>

TABLE 3.1

Frequency of MPQ Descriptors Used By Patients (n = 40).
Words only listed when reported by more than 20% of patients.
<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Count</th>
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<td>aching</td>
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<td>tender</td>
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<td><strong>Other descriptors</strong></td>
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Aetiology of Atypical Odontalgia

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<th>Allerbring et al., (1993) (n = 50)</th>
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<tr>
<td>other</td>
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</tbody>
</table>

3.5.3 Efficacy of capsaicin

Results of this study showed topical capsaicin to have similar efficacy in pain reduction compared with the work of Epstein et al., (1994) in treating "oral neuropathic pain". While
37% of patients received no benefit from capsaicin, 63% had a positive, and frequently, a substantial response to the treatment. Review of the positive responders showed mean pain reduction was maintained although there was wide individual variation. The reason for this variable response is unclear based on the data obtained from this study; however, different underlying pathophysiological mechanisms would, most likely, be responsible (Dubner, 1991a). While peripheral nervous system effects of topical capsaicin are evident, additional benefit of the agent by axonal transport to the central nervous system would be likely. Three patients presenting at referral were on low dose tricyclic antidepressant medication and subsequently underwent concurrent capsaicin therapy. However, from this initial uncontrolled report, conclusions cannot be drawn at this stage as to the efficacy of a single therapy (capsaicin or tricyclic antidepressant) compared with both regimens together. Unfortunately, a review of the efficacy of tricyclic antidepressant therapy for the treatment of AO gives little data from which to draw conclusions - a follow up of 28 patients by Schnurr et al., (1992) and Brooke and Schnurr, (1993) with poorly specified data using tricyclic therapy, showed that 19 patients still reported pain, with seven patients reporting "constant" pain.

A difficulty encountered in this study assessing capsaicin efficacy was the ethical requirement to treat the TMD component when present. TMD therapy consisted of intensive physiotherapy (ultrasound and laser) and extension exercises for the involved muscle groups. Patients were advised, if possible, to institute physiotherapy post-capsaicin treatment. However, some patients used physiotherapy before or during the capsaicin trial, thus limiting accurate evaluation of the capsaicin treatment. A further problem encountered
was the almost impossible task of employing a suitable placebo in the oral cavity - an agent that generated a chilli-like sensation or experience, yet did not elicit any known sensory nervous system effect. It should be noted that strictly controlled long term studies assessing treatment procedures for chronic pain are fraught with difficulty - some patients (and referring doctors) embarking on their own protocols. Both Brooke et al., (1993) and Feinmann, Harris et al., (1993) have reported on the difficulties of orofacial pain management, particularly in those patients with a long and complex pain history involving psychosocial problems (Feinmann, 1993). Fortunately, however, in this study, most patients claimed they could distinguish between the benefit of physiotherapy for TMD (facial / extraoral pain reduction) and the benefit from capsaicin treatment (intraoral pain reduction). While peripheral nervous system effects of topical capsaicin are evident, additional benefit of the agent by axonal transport to the central nervous system would be likely. With topical capsaicin offering itself as a simplistic and non-invasive technique, it should be considered an important therapeutic regimen in the treatment of AO if controlled, blinded studies confirm these preliminary data.

3.5.4 TMD considerations

Difficulty in diagnosing AO could be attributed to the secondary TMD that was present. The majority of patients with AO presented with TMD signs and symptoms (Table 3.3). TMD would be generally considered among dental practitioners as relatively straightforward to diagnose and treat. However, without corresponding treatment for AO,
little relief was obtained in patients, and would account for the failure of conventional TMD
treatment instituted by referring practitioners. Consequently, the problem continues to
bewilder most dental practitioners. Nearly all patients with AO-TMD stated that the TMD
signs and symptoms occurred after the onset of intraoral pain (AO). The appearance of
TMD could certainly be accounted for by the multiple teeth that were extracted in an
attempt to alleviate pain, exacerbated by the patient being unable to tolerate a denture or
occlusal splint, due to hyperalgesia of the extraction site(s). Often, patients had whole
quadrants of teeth decimated by dental treatment. A typical case history might involve
multiple restorations, followed by root canal therapy, apicectomy, extraction, and
exploration and curettage. This treatment rationale is based on the outdated Cartesian
model of pain, whereby removal of the peripheral source of the patient’s reported pain is
expected to remove the pain along with the "amputated" body part. Several patients
claimed that "jaw clenching" and "grinding my teeth" helped them cope with the constant
intraoral pain. Patients suffering from a dual complaint (AO-TMD) have been reported in
27-50% of subjects (Schnurr et al., 1992), bruxism identified in 45% of AO patients
(Rees et al., 1979), and TMD as an associated condition in AO (Marbach, 1993c). Table
3.3 shows the frequency of TMD signs and symptoms present in the AO-TMD group.
Animal studies by Sessle et al., (1986) and Sessle (1987) have provided a possible
explanation as to the frequent occurrence of TMD - there is convergence of afferent fibres
from muscles, cutaneous tissues and tooth pulp in the subnucleus caudalis (medullary dorsal
horn) that may be responsible for the spread and referral of pain. Whether primates exhibit
similar neurophysiology remains to be shown; however, the work by Sessle et al., (1986)
questions the discrete classification of dermatomes based on cutaneous receptive field properties.

3.5.5 Sympathetic nervous system contributions

Results of phentolamine infusions (0-80% pain reduction), although performed in a limited number of patients, indicated that SMP is a frequent but variable component of AO. Lynch et al., (1996) recently reported a similar variable pain reduction response of SMP from stellate ganglion block in their study of oral neuropathic pain. This provides further evidence that AO is a form of oral neuropathic pain, or that both are the same condition (Marbach, 1993b; Graff-Radford et al., 1993; Epstein et al., 1994; Lynch et al., 1996). SMP is defined as pain that is maintained by sympathetic efferent innervation or by circulating catecholamines. Pathophysiology of SMP involves coupling between sympathetic and somatosensory pathways that has been postulated to occur at peripheral nociceptors, the dorsal root ganglion with sprouting of noradrenergic perivascular axons (McLachlan, Janig et al., 1993), and central spinal cord sites (Roberts, 1986). Both direct and indirect methods of excitation of peripheral nociceptors by noradrenaline have been proposed. Following nerve damage or chronic inflammation, a subset of C-polymodal nociceptors has been shown to develop sensitivity to sympathetic stimulation (Sato et al., 1991; Sanjue et al., 1989) and thus may be directly stimulated by noradrenaline. Alternatively, noradrenaline may act indirectly via release of prostaglandins that in turn stimulate the nociceptor (Levine and Taiwo, 1990; Tracey, Cunningham and Romm, 1995). There is now an increased awareness of the role of the sympathetic nervous system in a variety of neuropathic pain states such as post-herpetic neuralgia, central nervous system lesions and
"amputation" (phantom pain) syndromes (Walker et al., 1997). Histological studies of neural innervation of the orofacial region have suggested sympathetic involvement in "causalgia" (Hoffmann and Matthews, 1990; Gregg, 1990a, 1990b). SMP has been linked in the past with "reflex sympathetic dystrophy" and "causalgia", now designated Complex Regional Pain Syndromes (CRPS) I and II, respectively (Merskey et al., 1994). The IASP has defined CRPS Type I "as 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. It is associated at some point with evidence of oedema, changes in skin blood flow, abnormal sudomotor activity in the region of pain, or allodynia or hyperalgesia; and have defined CRPS Type II as “burning pain, allodynia, and hyperpathia usually in the hand or foot after partial injury of a nerve or one of its branches” (Merskey et al., 1994). 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 alldynia / 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 and abnormal sudomotor and motor activity. 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 patients who will benefit from sympatholysis.

3.6 Conclusion
Over 82% of patients had pain that migrated from a single tooth site to multiple sites of teeth, and also had widely diffuse pain throughout the gingivae and mucosa. In this study,
AO occurred in all quadrants with no predisposition in the maxilla or mandible, in contrast to previous data (Pöllmann, 1993). The traditional representation of the afferent nervous system refers to a 'hard-wired' system with pain unable to cross anatomical boundaries such as the midline. However, recent data have shown that "peripheral sensitisation" is associated with localised or "primary hyperalgesia", and "central sensitisation" is associated with "secondary hyperalgesia"; these may spread vertically and may cross the midline. Afferent pathways have the potential to exhibit 'plasticity' following peripheral nerve damage (Dubner, 1991b; Hökfelt, Zhang and Weisenfeld-Hallin, 1994). Chronic pain states usually have a peripheral and central nervous system component. This would explain the partial success in previous trials of tricyclic antidepressants (Rees et al., 1979) for the central component, and the similar partial success in this study from local topical applications of capsaicin for the peripheral component. It is also possible that capsaicin may have central effects through axonal transport from peripheral administration. The peripheral pain component varied markedly from 0-100%, based on the results of EMLA application. However, pain reduction from the EMLA application did not necessarily predict the success of capsaicin treatment. Variable results of the phentolamine test showed that a sympathetic contribution is present in some (but not all) patients, adding to the complexity of AO and suggesting that optimum treatment requires several diagnostic procedures.

Finally, to further complicate matters in addressing this condition, there have been changes in the nomenclature since AO was first reported. Originally, the condition was described by some authors as AO in response to the 'atypical' nature of the condition; this term was
subsequently listed in the IASP taxonomy (Merskey et al., 1994). Other terms used for AO have included idiopathic odontalgia (Harris, 1974), neurovascular odontalgia (Mahan et al., 1991), phantom tooth pain (Marbach, 1978), and more recently, oral neuropathic pain (Marbach 1993a, 1993b; Epstein et al., 1994; Lynch et al., 1996). However, for some patients AO could arguably be termed as a CRPS. Diagnostic criteria for CRPS (I and II) include oedema, changes in skin blood flow and abnormal sudomotor and motor activity. While thermographic data may support some diagnostic criteria for AO as meeting the criteria for CRPS, other features, such as increased sudomotor activity, denote the difficult nature for satisfying the current criteria of CRPS in the oral cavity. Further studies of this condition may be confused by past and recent nomenclature changes, particularly by practitioners unfamiliar with AO. Clearly, consensus among researchers and clinicians as to the final name AO is to be known by needs to be addressed.

This study has analysed the largest group of patients with AO reported in the literature to date and illustrates the complexity of chronic pain, particularly in the orofacial region. Due to our current lack of understanding of AO, studies are warranted of the epidemiology and causation of this distressing condition. Capsaicin appears to be a promising agent in treating AO based on the evidence from this initial uncontrolled report, since concurrent treatment regimens (such as tricyclic antidepressants) were restricted for the majority of patients in this study to provide some measure of control. However, blinded, controlled studies of capsaicin are still required to assess its definitive therapeutic effect. The current treatment for other types of neuropathic pain, such as phantom limb pain and post-herpetic neuralgia, includes membrane-stabilising drugs such as mexiletine, and drug combinations of
anticonvulsants and tricyclic antidepressants (Presley et al., 1992). Recent pilot data have also indicated the utility of mexiletine for treating oral neuropathic pain and the lignocaine infusion as a diagnostic procedure (Saxen, Adams et al., 1994). Unfortunately, patient non-compliance due to drug side effects is common, thus reducing the efficacy of the regimens. Future modalities for the treatment of severe neuropathic pain of body and limbs (and possibly oral neuropathic pain) will likely include spinal cord stimulation and long-term matrix-formulations of drugs via intrathecal administration. This study and previous work show AO to have multiple components including hyperalgesia (primary and secondary), allodynia, SMP and myofascial pain. In addition, psychological factors of chronic pain such as depression and 'stress' (66% of patients in this study) are present. Moreover, associated pain behaviour and variable pain-coping skills further complicate evaluation of the patient, and his / her respective individual response to treatment. Further studies of AO are warranted, and due to the multifactorial nature of this pain condition, it is highly desirable that AO patients have a multidisciplinary approach to diagnosis and treatment.
TABLE 3.3

Frequency of TMD Signs and Symptoms in AO-TMD Patients (n=30).

<table>
<thead>
<tr>
<th>TMD sign / symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>facial / jaw pain</td>
<td>87</td>
</tr>
<tr>
<td>neck pain</td>
<td>70</td>
</tr>
<tr>
<td>bruxism</td>
<td>60</td>
</tr>
<tr>
<td>headaches / earaches</td>
<td>57</td>
</tr>
<tr>
<td>Symptom</td>
<td>Frequency</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Temporomandibular joint pain</td>
<td>50</td>
</tr>
<tr>
<td>Clicking of temporomandibular joint</td>
<td>50</td>
</tr>
<tr>
<td>Difficulty in chewing</td>
<td>47</td>
</tr>
<tr>
<td>Facial / masticatory muscle tension</td>
<td>47</td>
</tr>
<tr>
<td>Restricted oral opening</td>
<td>43</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>37</td>
</tr>
<tr>
<td>Teeth chipping / wearing down</td>
<td>37</td>
</tr>
<tr>
<td>Dizziness</td>
<td>33</td>
</tr>
<tr>
<td>Unpleasant taste</td>
<td>33</td>
</tr>
<tr>
<td>Difficulty in breathing through nose</td>
<td>30</td>
</tr>
<tr>
<td>Tingling sensation in face</td>
<td>27</td>
</tr>
<tr>
<td>Numbness in face</td>
<td>13</td>
</tr>
<tr>
<td>Locking of jaw</td>
<td>7</td>
</tr>
</tbody>
</table>
CHAPTER 4

STUDY 4: SALIVA AS A POTENTIAL MATRIX FOR OBJECTIVE PAIN MEASUREMENT

4.1 Introduction

The previous studies on different orofacial pain conditions, particularly AFP and AO, illustrates the difficulty often encountered by clinicians in diagnosing patients. It was found that many of these patients had in fact two conditions - the primary condition and the secondary condition in the form of an associated TMD. The difficulty faced by the previous practitioners in diagnosing multiple conditions probably delayed treatment for some patients. Moreover, the psychological state of the patient may have greatly influenced the reported pain intensity potentially leading the clinician to institute inappropriate treatment such as choice and dosage of drugs. These problems could be addressed, in part, if simple, reliable and objective pain measurement were possible and saliva has recently been suggested as a matrix worthy of further assessment for diagnosis of different pain states. The work in this chapter is a preliminary investigation assessing saliva as a possible matrix for different pain states.

4.1.1 Historical perspectives of saliva

The saliva of Christ was attributed with miraculous properties: “When he had thus spoken, he spat on the ground, and made clay of the spittle, and he anointed the eyes of the blind man with the clay. And said unto him, Go, wash in the pool of Siloam. He went his way therefore and washed, and came seeing.” (John 9:6-7; cited by Raimer Smith, 1950). Prior
to the 17th century, the salivary glands were thought to be organs that “strained off the evil spirits of the brain”. Moreover, the absence of salivary flow (through anxiety arising from guilt) in an individual, constituted a 'lie detector' test for the early court systems (Mandel, 1990). Although the knowledge that salivary glands do not act primarily as filtering organs was evident in the 1860s, scientific studies into saliva, with definitive aims, did not begin until the mid-1950s.

4.1.2 Saliva as a matrix and diagnostic fluid

Initial interest in saliva was centred on the recognition of its importance to dental caries, evident through its buffering capacity and its constituents. The critical roles of saliva for oral health research have primarily included caries prevention and the maintenance of mucosal and gingival tissue integrity for periodontal health. However, the biofluid underwent a resurgence of interest among researchers, spurred by the ease and non-invasive technique(s) in obtaining samples. In the 1970s, saliva was used as a sample matrix for drug assays where, in pharmacokinetic studies, it was regarded as being comparable with an ultrafiltrate of plasma. More recently, lower limits of detection and better separation technology particularly by high-performance liquid chromatography (HPLC), have allowed a greater understanding of the fluid’s biochemical constituents (Distler and Kröncke, 1987; Perinpanayagam, Van Wuyckhuyse et al., 1995). Systemic diseases that can affect salivary glands and saliva include Sjögren’s syndrome, rheumatoid diseases, sarcoidosis, hypertension, malnutrition, hormonal dysfunction (diabetes, thyroiditis, pancreatitis) and neurological diseases (cerebral palsy, Bell’s palsy, Parkinsonism) which have been well
documented (Mandel, 1990). Saliva is underutilised as a diagnostic fluid by clinicians when compared to other biofluids such as blood, cerebrospinal fluid (CSF) and urine.

A particularly important focus of pain research involves biochemical mediators in pain initiation and signalling. There is now substantial evidence that certain biochemical mediators, including prostaglandins (PGs), histamine, serotonin, substance P and bradykinin, can produce pain or alter the intensity of pain. It has been suggested that the determination of concentrations of these substances may lead to a ‘biochemical profile’ of different forms of pain (Rimon, Le Greves et al., 1984; Quinn and Bazan, 1990; Aghabeigi, Feinmann et al., 1993; Israel, 1994). Saliva has been suggested as a suitable diagnostic fluid to assay for mediators of chronic pain. For example, pilot data suggested that mean immunoreactive substance P concentrations in plasma and saliva for a group of patients with chronic back pain were significantly lower than those in a control group of healthy volunteers (Parris, Kambam et al., 1990). Similar differences in CSF concentrations of substance P between healthy controls and chronic pain patients have been reported (Almay, Johansson et al., 1988). Other studies have evaluated salivary constituents for a number of conditions: amino acid levels in periodontal disease (Syrjänen, Alakuijala et al., 1990), PGE₂ in migraine patients (Tuca, Planas and Parellada, 1989), PGE₂ and PGF₂α in cystic fibrosis patients (Rigas, Korenberg et al., 1989), magnesium levels in migraine sufferers (Gallai, Sarchielli et al., 1992) and salivary components in leukemia (Månsson-Rahemtulla, Techanitiswad et al., 1992).
4.1.3 Advantages in the analysis of saliva

The advantages of the collection of saliva for diagnostic purposes are considerable, especially when compared with the usual methods of blood and CSF sampling. From the investigator’s experience, patients and research volunteers have excellent compliance in donating saliva. Repeat samples can be obtained from both clinical and research subjects over long periods, without the need for cannulae and associated equipment. For the healthcare worker or researcher, saliva collection is of low risk and totally avoids the risk of needle-stick injury as a subject can donate directly into a specimen receptacle, thereby avoiding contact for the healthcare worker altogether. From a clinical perspective, saliva could be considered as the ideal medium, if its constituents reflect the health of the patient; indeed, saliva could be a crucial biofluid for improving research methodology in studies when biochemical assessment of pain or nociception necessitate a pain-free method of biofluid collection. For example, systemic concentrations of algogens in plasma and CSF samples could be affected by the method potentially causing the local release of algogens at the site of cannulation, thereby producing spurious data. Thus, in the area of pain research, saliva may have distinct advantages over invasive techniques if salivary concentrations of biochemical constituents correlate with the respective plasma concentrations and / or provide information about local concentrations pertaining to the local conditions.

4.2 Aim

The aim of this preliminary investigation was to compare the chromatographic profiles of saliva from several patients with different pain states. This would lead to further studies of one inflammatory mediator, namely bradykinin, in later parts of this thesis.
4.3 Patients and methods

Patients

A limited, uncontrolled pilot study of five subjects was carried out to evaluate salivary chromatographic profiles as potential ‘fingerprints’ of pain states. No subject was taking medication thus negating the potential for any drug to influence salivary constituents. Subjects were asked to rate his / her pain as “no pain”, “mild to moderate pain” or “severe pain”. Briefly, the subjects were: subject 1, a healthy 37 year old male; subject 2, a healthy 39 year old male; subject 3, a 64 year old female with a 2 year history of cancer of the colon and in “no pain”; subject 4, a 58 year old female with a 3 year history of lung cancer and in “severe pain”; subject 5, a 39 year old male with a 10 year history of back pain and in “severe pain” (Table 4.1).

Methods

The study utilised HPLC and subjects donated 1 mL of unstimulated, mixed saliva that was prepared as described in section 7.7.2; 10 µL of saliva was injected into the HPLC. HPLC conditions were a mobile phase consisting of 25% acetonitrile, 75% 10 mM Na$_2$HPO$_4$/NaH$_2$PO$_4$ (pH 5.5) at a flow rate 1.0 mL / minute; the UV detector was set at 215 nm and a Macrosphere WCX stainless steel column 7 µm particle size, 300 Å pore size, 150 mm ⊙ 4.6 mm internal diameter (Alltech, Deerfield, Illinois, USA) was used to separate the constituents.

4.4 Results
The chromatographic profiles of the group have been overlaid in Figure 4.1. The healthy controls have similar chromatograms. The patients suffering from pain have clearly different profiles to the controls. There are noticeable differences in the concentrations of several constituents of interest, namely in the peaks eluting at 6.5, 15.0, 19.0 and 22.5 minutes.

4.5 Discussion

In undertaking this pilot study it was necessary to assess pain conditions and pain intensity without the influence of drug effects on salivary constituents. In recruiting subjects for this study, not surprisingly, there were only few patients with pain states or disease conditions who were not taking any form of medication. While this pilot study was uncontrolled and the number of subjects was limited, its purpose was simply to compare different basal profiles i.e. was a ‘fingerprint’ of pain apparent using HPLC? Clearly, the comparison of the chromatograms indicate that further work is warranted to identify the constituents (indicated by the major peaks on chromatograms). Within the scope of this thesis, a focus on bradykinin as a possible candidate for one of these markers was suggested from the literature and was subsequently undertaken; the results are presented in the next chapter.

This study, while lacking definitive data, suggests that a further controlled study with a larger cohort would be interesting. If these pilot study ‘fingerprints’ are representative of different pain states, then more detailed biochemical studies may offer several exciting possibilities. First, identification of increased substances using chromatography and mass spectrometry may help in the quest for more precise analgetic regimens for various pain states calibrated biochemically. Second, physical and psychological components of chronic pain may be
evaluated. Third, pain relief given to those who cannot report pain (infants, mentally handicapped patients etc) may be evaluated. Fourth, chromatographic-mass spectrometric of saliva may provide more information on analgetic drug pharmacokinetics and pharmacodynamics by providing a quantitative measure of drug effect.
### TABLE 4.1

**Subject Data and Pain Variables for Study 4**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pain State</th>
<th>Duration of Pain (years)</th>
<th>Pain Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>male, 37 yrs</td>
<td>healthy control</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>male, 39 yrs</td>
<td>healthy control</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>female, 64 yrs</td>
<td>cancer of colon</td>
<td>2</td>
<td>“no pain”</td>
</tr>
<tr>
<td>female, 58 yrs</td>
<td>lung cancer</td>
<td>3</td>
<td>“severe pain”</td>
</tr>
<tr>
<td>male, 39 yrs</td>
<td>back pain</td>
<td>10</td>
<td>“severe pain”</td>
</tr>
</tbody>
</table>
Figure 4.1
Chromatograms of 5 subjects: 2 healthy controls, 1 patient with cancer and “no pain”, 1 patient with cancer and “severe pain” and 1 patient with “severe” chronic back pain. 10 µL injection of saliva from each subject was prepared as described in section 7.7.2. HPLC conditions were: mobile phase consisting of 25% acetonitrile, 75% 10 mM Na₂HPO₄ / NaH₂PO₄ (pH 5.5); flow rate 1.0 mL / minute; UV detector set at 215 nm; Macrosphere WCX stainless steel column 7 µm particle size, 300 Å pore size, 150 mm ⊙ 4.6 mm internal diameter.
CHAPTER 5

BRADYKININ LITERATURE REVIEW AND STUDY 5

Literature Review

5.1 Introduction

There have been two extensive reviews of bradykinin (Regoli and Barabé, 1980; Schachter, 1980) detailing the history of bradykinin and its main biological actions which are cardiovascular effects and algogenic actions: the following summary is based heavily on these reviews.

The discovery of the kinins body began with the French surgeons Abelous and Bardier who observed transient hypotension in humans with intravenous injections of fractions extracted from human urine. Later work carried out by Frey and associates in the 1920s and 1930s characterised the hypotensive substance. They showed that similar material could be obtained from saliva, plasma and, in particular, the pancreas which proved to be rich source of the material and which consequently was named 'kallikrein'. By 1937, Wehle, Gotser and Keppler had established that kallikreins have an indirect enzymatic effect by splitting off a pharmacologically active substance, subsequently named “kallidin” by Wehle and Berrick in 1948. Kallidin was shown to be a polypeptide cleaved from a plasma globulin termed kallodinogen. Later, Rocha e Silva and coworkers reported that the venoms of certain snakes acted on plasma globulin, to produce a substance that caused a slow contraction of the gut and lowered blood pressure. Due to the slow gut response, the substance was termed “bradykinin”; a term derived from the Greek word "bradys" meaning slow and
"kinein" meaning to move. It was suspected and later confirmed that kallidin (the traditional name as opposed to lys-bradykinin) and bradykinin were identical.

Bradykinin is a nonapeptide and is formed by the action of enzyme kallikreins on high molecular weight (HMW) kininogen. Plasma HMW kininogen forms bradykinin and tissue kallikreins form the decapeptide kallidin (lys-bradykinin) from low molecular weight (LMW) kininogen. Pharmacological properties of bradykinin include increased capillary permeability, production of oedema and the initiation of pain. Some responses of bradykinin are mediated by PGs. Regoli et al., (1980) have published an extensive review of bradykinin and its known pharmacological effects: i.e. as an algogen, involvement in the inflammatory processes, mediation in reactive hyperthermia in exocrine glands and apparent involvement in control of blood pressure through its hypotensive action. Bradykinin has also been implicated in pathological states and inflammatory diseases such as rheumatoid arthritis (Hargreaves, Troullos et al., 1988; Uhl, Singh et al., 1992) and myocardial ischaemia (Kurita, Takase et al., 1992); it has also been shown to modulate the release of noradrenaline from peripheral sympathetic nerve terminals (Llona, Galleguillos et al., 1991).

5.2 Biochemistry of bradykinin

Due to past complexities in the isolation and identification of plasma kinins, the nomenclature became confused. It is now generally accepted that the term “kallidin” should be restricted to the decapeptide, while the term “bradykinin” has been retained for the nonapeptide. Bradykinin has the following amino acid sequence: Arg - Pro - Pro - Gly - Phe - Ser - Pro - Phe - Arg. Kallidin has an additional N-terminal lysine and is also referred to as lys-
bradykinin. Bradykinin is a highly charged peptide that is unlikely to cross the cell membrane and is considered unlikely to be subject to breakdown from intracellular proteases.

Kinins are formed in biological fluids by activation of kininogens and differ from endogenous agents (neurotransmitters and autacoids) that are synthesised and stored in specialised cells. Kininogens exist in two forms: LMW kininogen (MW 48,000) and HMW kininogen (MW 100,000). Activation of kinins from kininogens is initiated by kallikreins produced by liver (plasma kallikreins) and exocrine glands (glandular kallikreins). Kallikreins are found in the inactive form (liver, pancreas and intestine) and the active form (kidneys and salivary glands). Normal blood contains all essential ingredients for the formation of massive amounts of bradykinin but usually very little bradykinin is formed, as plasma kallikrein is present in an inactive form, prekallikrein. Conversion of prekallikrein to kallikrein with resultant formation of bradykinin is readily brought about by various factors. These include substantial changes in pH or temperature and by contact with negatively changed surfaces such as glass or kaolin or by biological materials (collagen and the basement membrane) which are readily exposed by tissue damage. Many of the factors that activate kallikrein are involved in Hageman factor (HF)-initiated coagulation and fibrinolysis. Thus, the formation of bradykinin involves a cascade of enzymatic reactions triggered by activation of HF. Kinins formed in plasma are rapidly inactivated by enzymes (kininases) present in plasma and tissues. Metabolism of bradykinin occurs at the C-terminal end by kininase I and kininase II. Kininase I (carboxypeptidase N, MW 280,000) removes the C-terminal Arg from bradykinin to form (1-8) bradykinin: this occurs in plasma and is responsible for 80 - 90% of bradykinin destruction. (1-8) bradykinin is then further metabolised to form (1-5)
bradykinin from tripeptidase activity. Kininase II is a carboxydipeptidase (glycoprotein MW 129,000 - 480,000) that cleaves Phe-Arg to metabolise bradykinin to (1-7) bradykinin and accounts for the remaining 10 - 20% of breakdown. Kininase I is present in blood, while kininase II is predominantly located in viscera. Plasma bradykinin has a very short half-life, 15 - 18 seconds in the dog and cat, and a few seconds in the human lung (Mirgorodskaya and Shevchenko, 1992). Endopeptidase and chymotrypsin are also involved in bradykinin metabolism, but their specific contribution is unknown (Casarini, Alves et al., 1992).

Bradykinin exists in solution as a nearly-random coil with no fixed relationship between its ends and has neither an α-helix nor a β-pleated sheet structure (Brady, Stewart and Ryan, 1970).

5.3 Biological actions and receptor sites of bradykinin

5.3.1 Cardiovascular effects

Bradykinin has historically been associated with cardiovascular regulatory functions as one of its prime biological actions. It causes a rapid and reversible hypotension in animals and humans when injected intravenously. Kinins are potent vasodilators, approximately tenfold more potent than histamine, and can stimulate the release of histamine from mast cells. Vascular beds in muscles, kidneys and viscera are affected by bradykinin, and dilation of cerebral vessels may result in headache.

The direct action of kinins on arteriolar smooth muscle causes a rapid decrease in both systolic and diastolic blood pressures. The kinins increase permeability of the microcirculation; however, large arteries and most veins undergo contraction as observed
when bradykinin is injected into the carotid artery of the cat and dog. The effect on the microcirculation is preferential to small venules, rather than to capillaries, and causes separation of endothelial junctions. This result, coupled with an increased hydrostatic pressure gradient, causes oedema.

5.3.2 Algogenic actions

There is evidence supporting a role for the kallikrein / kinin system in spinal nociceptive neurotransmission and bradykinin has also been implicated as a putative neurotransmitter. The presence of bradykinin-receptor binding sites in the substantia gelatinosa, dorsal root and dorsal root ganglion of the guinea pig has been documented. Bradykinin immunoreactivity is present in both the spinal cord and CSF of several species including humans. It is thought to be of pharmacological significance that the mammalian central nervous system has the capacity to synthesise, metabolise and store both bradykinin and kallidin. Nociceptive responses and / or pain occur when the kinins are injected intraperitoneally into animals or into arteries supplying skin, muscle or various viscera of humans, resulting in an increase in the discharge of afferent sympathetic fibres. Bradykinin is a potent mediator of pain and bradykinin antagonists relieve pain (Steranka, Manning et al., 1988). However, others have demonstrated antinociceptive activity of bradykinin. Lanueville, Reader and Couture (1989) placed iontophoretic applications of bradykinin onto single dorsal horn neurones (rat spinal cord) that had been excited by noxious thermal stimulation to skin. The results showed slowed excitation of neurons as demonstrated by an increased reaction time compared with basal measurements for tail withdrawal. However, the mechanism by which bradykinin exerts this antinociceptive activity remains unresolved.
Intrathecal administration of captopril, an inhibitor of kininase II, prolonged the antinociceptive effect of bradykinin, suggesting that metabolically stable bradykinin agonists may represent a new class of promising intrathecal / epidural analgesics (Lanueville et al., 1989). The biphasic algogenic / analgesic action of bradykinin has also been observed in rats, respectively, two exciting states and one sedative state were described following administration of bradykinin to rat lateral ventricles (Yazaki, 1989).

The plasma kinins are recognised as powerful algogenic agents and cause an intense, burning pain when applied to the exposed base of a blister, and a throbbing, burning pain in the hand when injected into the brachial artery. Kinins can also promote the production and / or release of PGs in vivo from rabbit lung and heart, dog kidney and spleen, and uterus (Morimoto and Oku, 1995). There has also been the suggestion that bradykinin stimulates the accumulation of cyclic-AMP, thereby promoting smooth muscle contraction, through the induced release of PGs (Hillier, 1988). Bradykinin is involved in a positive feedback loop by activating macrophages to release cytokines, which in turn amplify responsiveness of bradykinin target tissues. The kinins, in relatively high concentration, can stimulate ganglion cells and elicit discharge of catecholamines from the adrenal medulla. Kinins, unlike angiotensin, do not stimulate the release of noradrenaline from sympathetic nerve terminals, rather they tend to reduce it. The injection of bradykinin into the cerebral ventricles causes a wide spectrum of behavioural, autonomic and electroencephalographic (EEG) effects. In oedematous tissue, activation of kallikreins occurs and degradation of kinins may be reduced by the decreased pH of the fluid, thus prolonging pain (Burch, Connor and Tiffany, 1989).
5.3.3 Receptor sites

Initially, receptors for kinins were classified as being P (mediating pain) or S (mediating swelling) types (Sicuteri and Rocha e Silva, 1970). However, Schild's criteria has been widely adopted for receptor sites (Regoli et al., 1980). Specific criteria for receptor site classification include: (i) the order of potency of receptor agonists, (ii) the measurement of the affinity for competitive antagonists, and (iii) ligand-induced receptor desensitisation. Currently there are two recognised receptor sites: B1 (rabbit aorta) and B2 (rat kidney glomeruli, human fibroblasts, rabbit jugular vein, rat uterus, guinea-pig ileum, cat ileum, dog carotid artery and rat neuronal cell lines). The B2 receptor is a stable component of the cell membrane and is thought to be a glycoprotein, possibly in combination with lipid-detergent micelles and guanosine nucleotide-binding regulatory proteins (G-proteins) (Burch and Kyle, 1992; Roberts, 1989). The B1 receptors are poorly understood and appear to be absent in vivo; however, their appearance is induced after several hours exposure to noxious stimuli such as lipopolysaccharide. Intact kinins have little affinity for B1 receptor sites, but kininase I metabolites desArg^9^-bradykinin and desArg^10^-kallidin are potent spasmogens and B1 receptor sites have recently been reported on macrophages (Burch et al., 1992). Previous work (Tiffany and Burch, 1989) has suggested that bradykinin stimulates the release of interleukin-1 and tumour necrosis factor from macrophages, and proposed that cytokine release in inflammatory disease is mediated by a B1 kinin receptor.

The interaction of bradykinin with its receptor causes stimulation of intracellular phospholipase and a subsequent increase in intracellular Ca^{2+} (Roberts, 1989). Gammon,
Allen and Morrell (1989) have demonstrated the involvement of intracellular Ca\(^{2+}\) with phospholipase A\(_2\)-mediated release of arachidonic acid, augmented by PGs. Roberts (1989) has postulated a “superfamily” of receptor subtypes comprising of peptide ligand receptors including muscarinic, adrenergic and serotonergic types which can interact with G-proteins. The B2 receptor has several subtypes; at least two non-neuronal B2 receptors, and at least one B2 receptor unique to the neuronal system.

Recent interest has been generated in the possible role of bradykinin as a mitogen, and its link with oncogenic transformation. It has been hypothesised that stimulation of tumour cells is, in part, affected by local release of bradykinin from reactive inflammation. This concept was based on high levels of kinins in a human suffering from gastric cancer (Matsumura, Kimura et al., 1989).

5.3.4 Kallikrein content in exocrine glands

Exocrine glands (pancreas, kidney, salivary and sweat glands) have been found to contain prekallikreins and kallikreins, with kallikrein stored in cytoplasmic granules of cells in the submaxillary gland and pancreas (Bhoola, 1970). Historically, there has been controversy as to the action of the enzymes on glandular blood flow, as to whether its effect is major (Hilton and Lewis, 1955) or minor (Regoli et al., 1980). The presence of the enzymes also suggests regulation of salivary secretions, with a possible functional role in potassium concentrations. Schachter (1970) analysed the kallikrein concentration in saliva obtained from the cat submaxillary gland and showed that stimulation of the sympathetic nerve produced a much
higher concentration (up to 500 times) and output (up to 300 times) of kallikrein than parasymathetic stimulation.

5.3.5 Biofluid concentrations of bradykinin

Plasma concentrations of bradykinin measured by radioimmunoassay have shown large variations throughout the studies in healthy controls (Regoli et al., 1980). Hargreaves et al., (1988) measured plasma concentrations of bradykinin by immunoassay in acute and chronic inflammation. Results showed that concentrations of bradykinin were in the low femtomole / mL levels, but were elevated three-fold to four-fold during acute inflammation following oral surgery. Plasma concentrations were also increased two-fold to three-fold in patients suffering from rheumatoid arthritis, compared with control subjects.

Bradykinin has also been found in saliva, with research focusing on its role in localised periodontal inflammation (Sallay and Nador, 1950; Rodin, Kaslick et al., 1972). More recently, Omori, Takahashi et al., (1986a) claimed that bradykinin is present in low concentrations (0.9-7.3 ng/mL) in a control group of patients, who were in good general health and suffered no periodontal disease. Other studies have demonstrated high concentrations of kallikrein in saliva (Jenzano, Daniel et al., 1986; Jenzano, Brown and Mauriello, 1987; Jenzano, Hogan and Lundblad, 1992).

Bradykinin has also been measured in urine, nasal secretions and synovial fluid, again with wide variations within the control group, and between different studies (Regoli et al., 1980). It is speculated that some of this variability may be due to the rapid metabolism of
bradykinin, particularly arising from delay between biofluid collection, stabilisation of bradykinin and the immunoassay.

5.4 Aims

Bradykinin is an important mediator in pain pathways where its concentrations may reflect the state of nociceptive activation. However, it undergoes rapid metabolism in blood and its concentrations are therefore unlikely to be representative of such a state. Saliva is an alternative biofluid that is readily accessible and avoids potential intrinsic complications of blood sampling due to the local release of bradykinin from cannulation and the short time available to stabilise plasma bradykinin against metabolism, both of which will potentially lead to spurious bradykinin measurements. The aim of this investigation was to carry out a screening study on several patient groups for areas of potential investigation of salivary bradykinin. In particular, to assess any effect of age, sex or patient condition (acute inflammation, distant cancer or arthritis) on salivary bradykinin levels.

5.5 Patients and methods

Four groups of patients, a post-operative surgical group studied within two hours of surgery (n = 10), a post-operative surgical group studied 1-10 days after surgery (n = 12), a group with metastatic cancer (n = 12) and a group with arthritis (n = 8), were selected to determine salivary bradykinin concentrations. The details of patients' sex, age, medical history, current medical conditions and medication are given in appendices 7-10. Prescribed
medication was not changed during the study; however, it is acknowledged that certain drugs may have affected plasma and salivary bradykinin concentrations. For the post-operative surgical patients, the time was recorded between completion of surgery and saliva collection. For all patients, saliva was collected and analysed by HPLC as described in detail in section 7.7.2. Note that this method was finally adopted after considerable development (chapter 7).

5.6 Results

In the post-operative group where saliva was collected from 1-10 days post-operatively, 3/12 patients had measurable concentrations of bradykinin (141-171 ng/mL). In the acute post-operative group (saliva collected 0-2 hours post-operatively), 7/10 patients had measurable concentrations of bradykinin. The cancer group contained 4/12 patients with measurable bradykinin (188-1,381 ng/mL). None of the 8 patients in the arthritis group had measurable levels salivary bradykinin. A summary of results is found in Table 5.1 and for comparison includes the salivary bradykinin concentrations in a healthy control group obtained from chapter 10.

TABLE 5.1

Summary of Salivary Bradykinin Concentrations in Healthy Controls and Patient Groups (Data of control group obtained from results in chapter 10)
(* = bradykinin not detected: limit of detection = 7 ng / mL)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Postop. Group (0 - 2 hours)</th>
<th>Postop. Group (1 - 10 days)</th>
<th>Cancer Group</th>
<th>Arthritis Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>female male</td>
<td></td>
<td>female male</td>
<td>female male</td>
<td>female male</td>
<td>female</td>
</tr>
<tr>
<td>(n = 6) (n = 4)</td>
<td></td>
<td>(n = 6) (n = 4)</td>
<td>(n = 7) (n = 5)</td>
<td>(n = 6) (n = 6)</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>82 88</td>
<td>230 473</td>
<td>232 *</td>
<td>658 188</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>133 17</td>
<td>495 470</td>
<td>141 *</td>
<td>1381 *</td>
<td>*</td>
<td>*</td>
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<tr>
<td>*     *</td>
<td>721 *</td>
<td>271 *</td>
<td>437 *</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>*     *</td>
<td>335 *</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>*     *</td>
<td>831 *</td>
<td>*</td>
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</tbody>
</table>

5.7 Discussion

Saliva collected in the post-operative group between 1-10 days (see appendix 8 for the number of days after surgery when the sample was collected) showed 3/12 subjects with levels similar to healthy controls. However, in the post-operative group when samples were taken within two hours of surgery, the results showed detectable bradykinin in a greater
number of patients, and at higher levels. A number of possibilities may account for this. First, there appears to be a large increase in local tissue bradykinin concentrations immediately following surgery, as demonstrated by the third molar extraction surgical model (Swift, Garry et al., 1993). Therefore, in post-operative surgical patients sampled within two hours, higher blood concentrations of circulating bradykinin may possibly cause a resultant increase in salivary concentrations through diffusion or active transport of bradykinin from blood into saliva. This concept of obviously smaller, but still significant increases in plasma concentrations of bradykinin has been found when sampling from a distant site (Hargreaves et al., 1988). In contrast, however, two patients had major surgery (thoracotomy and abdominal surgery) without measurable bradykinin in saliva. Second, drug effects could alter the concentrations of bradykinin: atropine, in particular, has been proposed to stimulate the chorda tympani nerve to increase salivary bradykinin secretion via kinin formation (Hilton, 1970). Perioperative analgetic and / or anaesthetic drugs may depress its secretion. Bradykinin secretion may also be altered by the gastrointestinal response to presurgical ‘food deprivation’. Patients underwent a general anaesthetic procedure after the usual protocol of ‘nil by mouth’ for a minimum of six hours, in addition to the surgical operating time. A response to delayed food intake may possibly stimulate upper gastrointestinal tract (GIT) contractions, in turn requiring increased salivary bradykinin concentration, due to the smooth muscle effects of bradykinin.

Saliva samples from the cancer patients showed 4/12 subjects with measurable bradykinin in saliva: one female, in particular, demonstrated particularly high concentrations (1,381 ng/mL) when compared with healthy controls. The release of bradykinin into plasma from cancer-
induced tissue destruction and its subsequent passage into saliva may be responsible for high salivary concentrations of the peptide. The recording of pain intensity in patients by VAS was abandoned as many of the patients with cancer were in the terminal stages and were heavily sedated; similarly, many of the acute post-operative patient group were too sedated for useful responses. No subject in the arthritis group had measurable concentrations of salivary bradykinin. All of these patients were on numerous medications (appendix 10), including anti-inflammatory drugs which have been shown to reduce bradykinin concentrations (Swift et al., 1993). Due to the limited number of patients in this screening trial, possible factors that may influence salivary bradykinin concentrations such as specific medication or diet restriction, indicate that further investigation by controlled trials is necessary.

An important finding from this study was that several patients and healthy controls exhibited salivary bradykinin concentrations much greater than known blood concentrations of the peptide. In the light of these results, and the possibilities that bradykinin may have both algogenic and antinociceptive roles, it was felt that further study into bradykinin was warranted - to help determine whether there was a physiological role for salivary bradykinin. This study required the investigation of the pharmacological and pharmacokinetic profiles of salivary bradykinin which have not been previously published. To investigate its pharmacokinetics, a simple and reliable HPLC method was needed. Section 3 gives the background to published analytical methods for bradykinin, and details of the developed HPLC method as used in the present investigations, followed by studies of the
pharmacokinetics of salivary bradykinin and discussion of the possible physiological roles of
salivary bradykinin including its potential role in the development of orofacial pain.