FACTORS AFFECTING OUTCOME OF TREATMENT OF CRANIOFACIAL PAIN CONDITIONS:

1) TEMPOROMANDIBULAR DISORDER AND SMOKING

2) POSTTRAUMATIC HEADACHE AND NEUROPSYCHOLOGICAL FUNCTION

A PILOT STUDY

Angela N. Waciuk D.D.S

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Graduate Department of Dentistry
University of Toronto

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Angela N. Waciuk, Graduate Department of Dentistry, University of Toronto

Abstract

The objectives were to determine, 1) the effects of smoking on the response to treatment of TMD symptoms; 2) the presence of reduced cognitive function in PTH; 3) whether cognitive impairment can be used to predict poor treatment outcome for PTH ; and 4) to perform a descriptive assessment of the prevalence of signs and symptoms of TMD in the PTH population.

Hypotheses, 1) non-smokers will respond better to treatment for TMD than smokers; 2) poor neuropsychological test results are predictive of poor treatment outcome in a PTH population; and 3) patients with PTH will demonstrate signs and symptoms of TMD.

I found that smoking may be a modulator of pain in a TMD population and hence interfere with recovery. The prevalence of TMD signs and symptoms was lower than expected in a PTH population. The neuropsychological tests demonstrate a trend indicating possible use as predictors of treatment outcome.

Chapter One

Introduction

A) Smoking as a modulator of TMD pain

The use of tobacco has been established as a risk factor for cardiovascular disease, chronic obstructive pulmonary disease, and a spectrum of malignancies (Meltzer, 1994, Sherman, 1991) and more recently periodontal disease (Albandar et al., 2000; Bergstrom et al., 2000) and osteoporosis (Rapuri et al., 2000; Liu et al., 2001). It was not until the late 1970's that an association was described between smoking and low back pain (Frymoyer et al., 1980). Low back pain is a form of musculoskeletal pain and many epidemiological studies have been conducted over the last few decades to determine the association between smoking and this type of chronic pain. There are at least forty published epidemiological articles that have alluded to a possible link between smoking cigarettes and non-specific back pain. A very recent review concluded after evaluating thirty-eight studies that the available data are consistent with the notion that smoking is associated with the incidence and prevalence of non-specific back pain (Goldberg et al., 2000). They do point out though that it cannot be stated unequivocally that smoking preceded back pain. In contrast to these findings, another review of the literature, (47 studies reviewed) found no consistent statistically significant positive associations between smoking and low back pain (Leboeuf, 1999). In fact, the association, when present, was usually weak and clearly apparent only in large study samples. It was concluded that smoking should be considered a weak risk indicator and not a cause of low back pain. It has also been postulated by others that persons with musculoskeletal pain might experience more intense pain if they smoke, even if there might be an

equivocal effect on either incidence or prevalence. This study, based on a nationwide interview survey suggested that smokers do experience more intense pain than nonsmokers (Erikson et al., 1997). However, this association was only detected in young and middle-aged persons.

An association between smoking and the distribution of chronic pain in multiple musculoskeletal sites was found but only if, the neck or the lower back were involved, (Andersson et al., 1998). Interestingly, few studies have described smoking as a risk or exacerbating factor in locations other than the low back region. To date there are no studies to my knowledge that have reported a relationship, if any, between chronic TMD pain and smoking, and therefore this is an area that needs to be explored (TMD will be described in more detail in Chapter One, Section 1.B Part (iv)).

(i) Possible Mechanisms

a) Nicotine

There are various biological explanations for the suspected association between musculoskeletal pain and smoking. Two main hypotheses have been proposed. The first suggests that smoking induces reductions in blood flow, leading to hypoxia, or chemical changes that might lead to degeneration in muscles, joints, and discs (Brage & Bjerkedal, 1996). The second proposes that a central nervous effect might be involved. It has been implied that nicotine, through its excitatory effects, may alter the perception and threshold for pain, increasing the self-reporting of pain among smokers (Brage & Bjerkedal, 1996).

In contrast to findings suggesting that cigarette smoke increases pain perception, there are those who have found that nicotine is antinociceptive. In humans, it has been

observed that smoking has an analgesic effect, with an elevated tolerance or threshold to painful stimulation confirmed in several studies (Fertig et al., 1986, Perkins et al., 1994). Smokers smoking high-nicotine-yield cigarettes compared with abstinent smokers were found to have less pain (Lane et al., 1995). It is speculated that one effect that rewards smoking is a nicotine induced phasic blood pressure increase, which leads to baroreceptor stimulation and dampens pain perception. In a study of 120 subjects it was found that in heavy smokers, the nicotine induced phasic blood pressure increases might have baroreceptor dependent pain dampening effects, which might be among the reinforcing qualities of smoking (Rau et al., 1993).

b) Aryl Hydrocarbons

Another possible mechanism for pain modulation of cigarette smoke is the interaction of aryl hydrocarbon receptor (AhR) ligands and cytokines. Cigarette smoke contains a number of AhR ligands, including benzo(a)pyrene (BaP), and DMBA. It has been shown that dioxin (TCDD), a prototypical AhR ligand, is able to enhance carrageenan and dextran-induced paw edema in rats (Theobald et al., 1983; Katz et al., 1984). More recently, it was found that resveratrol, an AhR antagonist, was able to decrease hyperalgesia induced by carrageenan and TCDD in the rat hind paw (Gentilli et al., 2001). The sensitization of pain receptors causing hyperalgesia requires the release of hyperalgesic mediators. These mediators include prostaglandins and sympathomimetics, which are released subsequent to the release of cytokines such as interleukin-1b (IL-1b) and interleukin-8 (IL-8). Studies have shown that IL-1b, IL-8, TNF-alpha and IL-6 cause a dose-dependent hyperalgesia in rats (Ferreira et al., 1988; Cunha et al., 1991; Cunha et

al. 1992). More information on the putative mechanism of AhR ligands will be presented in the discussion.

Current evidence supports the theory that inflammation and pain are mediated through the release of cytokines. Aromatic hydrocarbons appear to increase the degree of pain experienced in a rat paw model. It is possible to suggest, based on the above findings, that through the binding of AhRs, cigarette smoke may induce the release of cytokines such as IL-1b and IL-8 and thereby induce an inflammatory state, which mediates pain. If this mechanism holds true then we would expect that in a TMD population, smokers would experience more pain and be less likely to respond well to treatment, notwithstanding the effects of nicotine. In a recent review article it has been suggested that inflammatory mediators, such as 5-HT and PGE_2, are present in painful masseter muscles in patients with fibromyalgia (Kopp, 2001). Patients with fibromyalgia often complain of symptoms from the orofacial muscles and thus frequently show signs of TMD (Kopp, 2001). These findings provide a possible role by which aryl hydrocarbons can up regulate inflammation and hence pain in the muscles of a TMD population.

B) Post-Traumatic Headache

Moderate to severe head injuries have been the focus of much research in the past with less emphasis on those suffering from more minor head injuries (MHI). Minor head injury can be described generally as those injuries where patients spent brief time, if any, in the hospital, made quick medical recoveries, and were discharged directly home without any perceived need for formal rehabilitation (Rimel et al., 1981). It is now recognized, however, that these patients appeared to be more or less 'normal' until they

attempted to resume their responsibilities at home, work or school, and when they did so, a significant number experienced great difficulty (Rimel et al., 1981). These individuals complained of inability to remember, concentrate, organize, handle a number of tasks at once, and get as much work done as efficiently as they used to. Their relationships with family, peers, and supervisors at work often suffered, and the subsequent development of psychological problems has been described. Indeed, these patients were often considered to be malingering. In such cases, the unique problem of MHI readily became apparent despite swift and complete physical recoveries, and despite no obvious neurological basis for their problems, these persons were experiencing significant cognitive, emotional, and behavioural deficits that seriously interfered with their ability to lead fully functional lives (Rimel et al.,1981).

The definition of a traumatic brain injury (TBI) has undergone a number of revisions over the years as research and clinical findings have provided more valuable information about such injuries. Until the early 1990's traumatic brain injury was classified as mild, moderate or severe based upon the initial Glasgow Coma Scale (GCS), duration of loss of consciousness (LOC), and duration of amnesia (Cope, 1990). A mild head injury was defined as an injury with an initial GCS of 13-15, post-traumatic amnesia of less than 24 hours and LOC less than 20 minutes (Cope, 1990). This definition was limited by including only those people who had a LOC and did not take into account the evidence that post-concussion symptoms can occur without LOC (Yarnell and Rossie, 1988; Radanov et al., 1992). In 1991, the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of

Rehabilitation medicine defined mild head injury as an injury with at least one of the following:

1. Any period of LOC of <30 minutes and GCS of 13-15 after this period of LOC.
2. Any loss of memory for events immediately before or after the accident, with post-traumatic amnesia of <24 hours.
3. Any alteration in mental state at the time of the accident (e.g. Feeling dazed, disoriented, or confused).
4. Focal neurological deficit(s) that may or may not be transient.(Berrol, 1992; Kay et al., 1993).

Unlike the previous definition, this definition encompasses a wide range of injury severity. It includes the patient being only dazed by the injury, or having a brief period of confusion without amnesia. It also includes the patient with a more significant MHI who is admitted to the hospital, may have permanent focal neurologic deficits, and may require short inpatient rehabilitation stay and outpatient treatment.

The 1991 National Health Interview Survey was analyzed to describe the incidence of mild and moderate brain injury in the United States (Sosin et al., 1996). From this survey it was estimated that 1.5 million non-institutionalized US residents sustain a non-fatal head injury each year. Motor vehicles were involved in 28% of the injuries, sports and physical activity were responsible for 20%, and assaults were responsible for 9%.

Each year approximately 70,000 to 90,000 individuals incur a TBI resulting in a long-term, substantial loss of function. The consequences of TBI include a dramatic change in the individual's life course, profound disruption of the family, enormous loss

of income or earning potential, and large expenses over a lifetime (National Institutes of Health, 1998). There are approximately 300,000 hospital admissions annually for persons with mild or moderate TBI, and an additional unknown number of TBIs that are not diagnosed but may result in long-term disability (National Institutes of Health, 1998).

The cognitive consequences of TBI are broad, and may occur singly or in combination and are variable in terms of their effects on individuals. As well, they change in severity and presentation over time (National Institutes of Health, 1998). Persons who sustain a head injury or cervical whiplash during a motor vehicle accident (MVA) often experience a variety of cognitive, emotional and physical symptoms that have been termed posttraumatic syndrome (Hickling et al., 1998). These symptoms can include headaches, dizziness, impaired concentration, memory difficulties, irritability, nausea, fatigue, and depression. Although the number and degree of posttraumatic symptoms vary among individual patients, headache, dizziness, cognitive difficulties, anxiety and depression are generally considered to be the most consistent. Posttraumatic headache is the most common posttraumatic symptom, occurring in approximately 30-50% of individuals following a MHI (Evans, 1992; Alves et al., 1986). Whiplash injuries, typically caused by MVA, also result in PTH (Jaspers, 1998). Whiplash refers to neck hyperextension followed by flexion, which occurs when a vehicle is hit from behind. Headaches have been reported in 82% of individuals immediately following whiplash injuries (Balla & Karnaghan, 1987).

Two major types of MHI exist, diffuse, and focal (Patt & Brodhun, 1999). It has been postulated that concussions were purely transient events akin to a "short circuiting", with no permanent damage to nerve cells in the brain (Kay, 1986), but this is not

necessarily the case. Using both autopsy studies in humans, and special cell staining techniques in animals, it has been demonstrated that even minor blows to the head can result in stretching and tearing of nerve fibers diffusely throughout the brain (Adams et al., 1982; Povlishock, 1993; Adams et al, 1989; Maxwell et al., 1991). These disruptions of nerve processes can only be seen microscopically. This microscopic stretching and tearing occurs because of the mechanical forces transmitted to the brain during trauma (Patt & Brodhun, 1999). The brain in not a hard, fixed organ but rather, it has a soft consistency and floats in cerebral spinal fluid within the hard bony skull. When the head is struck suddenly, strikes an object or is shaken, the mechanical force of this motion is transmitted to the brain. The brain mass itself moves, twists and experiences forces that cause movement of brain matter. The result of this motion is that the fine, threadlike nerve cells can become stretched. This stretching can temporarily alter the electrochemical function of the cells leading to altered consciousness. Most of the nerve cells will eventually return to normal function. Some of the stretched fibers, however, may be permanently damaged, either functioning abnormally or becoming totally inoperable (Kay, 1986). This would occur if the stretching of cells progressed to tearing, and, it has been suggested, provides the organic basis for the deficits experienced after mild diffuse head injury (King, 1997). Typically, neurological examination would reveal no evidence of brain damage.

(i) Effects of MHI/TBI on Cognition and Other Brain Functions

Because of the nature of diffuse MHI, the resulting deficits are not specific to particular domains of cognition. Rather, it is the overall speed, efficiency, execution and integration of mental processes that are disrupted in a general way. Persons with diffuse

MHI have impaired speed and capacity of information processing (Gronwall, 1991). That is, they process information less quickly, and react more slowly, and when faced with a choice they simply take longer to mentally process most tasks. Complex attention, in patients with MHI, is also impaired leading to difficulties in attention splitting among various tasks while efficiently executing complex operations that require multiple simultaneous decisions and choices. Such patients are however capable of executing any one of the operations independently. Diffuse MHI sufferers have learning and memory deficits and as a result do not have the ability to sort out, organize and quickly store complex incoming information (Levin et al., 1987). This causes such individuals to miss obvious details, and to be unable to recall information correctly. They also have deficits in integrative and abstract thinking, being unable to spontaneously make connections between ideas (National Institutes of Health, 1998).

Focal MHIs are injuries that result in specific neurological damage, which can be localized to a particular area of the brain (Patt & Brodhun, 1999). They involve grossly observable tissue damage and are more severe than the diffuse type. Previously two major types of lesions were thought to exist; 1) fronto-temporal lesions and 2) coup/contre-coup (blow/counter-blow) injuries. It is now generally accepted that the former lesions are more common and the term coup/contre-coup has slowly become obsolete. Fronto-temporal lesions occur commonly in acceleration-deceleration injuries. The Quebec Task Force adopted a definition of whiplash that states whiplash to be an acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear-end or side-impact motor vehicle collisions, but can also occur during diving or other mishaps (Spitzer et al., 1995). In the past decade, a number of researchers have argued

that cognitive difficulties reported by patients with whiplash are the result of a MHI sustained as a consequence of violent hyperflexion and hyperextension of the neck (Kischka et al., 1991; Radanov et al., 1992b). This injury has been postulated to occur on vehicular impact because the skull accelerates faster than the brain and subsequently impacts with the brain as it rotates backward or accelerates forward. Recently, a new model of whiplash injury has been proposed based on functional radiography and cinephotographic studies (Panjabi et al., 1998; Bogduk & Yoganandan, 2001). A distinct biphasic kinematic response has been found where the cervical spine undergoes a sigmoid deformation. Initially it forms an S-shaped curve with flexion at the upper levels and hyper-extension at the lower levels. In the second phase, all levels of the cervical spine were extended, and the head reached its maximum extension.

Injury to the fronto-temporal region leads to deficits primarily in the areas of learning and memory, planning and organization, attention and concentration and emotional control (Kay, 1986). Learning and memory are the hallmark of closed head injury and results from injury to the temporal lobes of the brain. These deficits are specific to new information, with old learning remaining intact. Injury to the frontal lobes is primarily associated with disruption of executive functioning, which is the process by which humans plan, organize, initiate, monitor and adjust thinking and behaviour. Patients often appear unmotivated and they fail to recognize that their performance is off. They may also fail to complete tasks, abandoning projects and never completing them. The fronto-temporal injury leads to problems of complex attention similar to that described for the diffuse MHI. In addition however, these persons may be highly distractible, going off on tangents and jumping quickly from idea to idea. Damage

to the orbital portions of the frontal lobes and basilar and medial aspects of the temporal lobes can result in disruption of emotions and behaviour. Emotions may suddenly and unpredictably erupt out of control, and patients might be irritable and quick to anger.

As previously mentioned, following a MHI, the most common symptom observed is the PTH (Packard, 1999). Paradoxically, the milder the head injury, the more frequently severe PTH is noted as a symptom (Yagamuchi, 1992). In fact, in many cases the incidence of headache is highest in those without loss of consciousness or post-traumatic amnesia.

(ii) Chronic Post-traumatic Headache (CPTH)

Chronic posttraumatic headache (CPTH) is defined by the Headache Classification Committee of the International Headache Society as headache occurring within 14 days of head injury (or regaining consciousness) and persisting for more than 2 months. The headache can be diagnosed with or without confirmatory signs: either loss of consciousness or posttraumatic amnesia greater than 10 minutes, or at least two abnormal studies, including skull radiograph, neuroimaging, neuropsychological tests or others (International Headache Society, 1988). PTH can be subdivided into several groups and people can suffer with one only or a combination of headache types including, tension type, post-traumatic migraine, cluster-like headaches or mixed headaches. The first three are similar to their non-traumatic counterparts. A tension type headache is commonly bilateral and characterized by a dull aching sensation often described as a pressure or band-like sensation around the head or as a weight on top of the head. Tension type PTH is the most frequent type of headache following MHI. It has been estimated that 85% of patients with post-concussion syndrome have tension-type

headaches (Mandel, 1989). Emotionally tense or stressful situations often accentuate these headaches. A migraine headache is typically unilateral and associated with nausea and sensitivity to light, sounds and smells (Weiss et al., 1991). The cluster headaches are periodic, recurring for weeks or months at a time, followed by periods of remission (Duckro et al., 1992). The pain is unilateral, commonly retro-orbital and associated with redness and watering of the eye as well as a stuffy nostril on the affected side. Headaches associated with the temporomandibular joint have been grouped with the tension type headaches (Fricton, 1989).

(iii) Motor Vehicle Accidents and Their Role in PTH

Motor vehicle accidents are common yet unexpected traumatic events. Their consequences can be chronic, disabling and catastrophic. In 1992, there were approximately 6 million motor vehicle accidents in the United States, costing an estimated $137 billion (US Department of Transportation, 1992). It has been reported that MVAs account for 42% of head and neck injuries (Povlishock, 1996). The reported rates of PTSD in victims of MVAs have ranged from 8% (Malt, 1993) to 46% (Mayou et al., 1999).

(iv) The Relationship Between Post-traumatic TMD and PTH

It might be postulated that when a PTH or any headache presents concurrently with TMD, poor outcome for the headache might be expected as a result despite intensive treatment and investigation (Fricton, 1989). Temporomandibular disorders are a collective term embracing a number of chronic pain problems that involve the masticatory musculature, the temporomandibular joint (TMJ), or both. A TMD may be defined as pain and/or dysfunction associated with the TMJ and/or the muscles of

mastication (Carlsson and DeBoever, 1994). TMD has been identified as a major cause of nondental pain in the orofacial region and is considered a subclassification of musculoskeletal disorders (Bell, 1989). In the past, TMD signs and symptoms were thought to be related to occlusal irregularities. This belief resulted in diagnostic errors, unnecessary irreversible dental treatments, and treatment failures. Based on both clinical and basic research, new concepts of pain and a broader understanding of chronic pain have resulted in the development and use of multidisciplinary teams for pain management. The origin of TMD symptoms is often idiopathic in nature. However, there is a small percentage of patients who manifest this condition in association with physical trauma, such as a blow to the face or a motor vehicle accident (Cohen & Hillis, 1979). Previous work has indicated that patients who present with pain following a MVA require more modalities of treatment and are less likely to have a reduction in symptoms as compared to an idiopathic TMD population (Brooke et al., 1977; Brooke & Stenn, 1978; Romanelli et al., 1992, Kolbinson et al., 1997b). It is now accepted that following a MVA, PTMD can develop (Goldberg et al., 1996; Kolbinson et al., 1997a). Like PTH, PTMD also responds poorly to treatment. Studies in our pain Unit at Mount Sinai Hospital, University of Toronto have shown that individuals with PTMD have cognitive and neuropsychological deficits that may explain, or at the very least, predict, poor response to treatment (Goldberg, 1996). In some cases, it is evident that the two conditions, PTH and PTMD, may co-exist but this is not identified until months or even years after the onset of either condition. This issue (ie co-morbidity) has not been elucidated clearly and indeed it is conceivable that this factor may play a role in making PTH (and/or PTMD) more difficult to treat.

(v) Use of Neuropsychological Tests for Monitoring and Predicting Treatment Outcome

The use of neuropsychological tests to assess and monitor treatment of brain-injured patients has been an accepted protocol for many years. Previous work has demonstrated how neuropsychological testing can be used to differentiate facial pain populations, and to predict treatment outcome (Goldberg et al., 1996). Tests used to assess reaction time, short and long term memory processes, as well as cognitive processes with various interferences can measure or estimate the deficits commonly observed in the post-traumatic headache and pain populations, as described above in the Section concerning PTMD and PTH. Various studies have confirmed that reaction times for performance of simple tasks triggered by computer generated visual stimuli were increased in head injured subjects compared to controls (Webster and Scott, 1988; Stuss et al., 1989; Stuss et al., 1985; Goldberg et al., 1996). Using these tests, subtle impairments in the rate of information processing and attention can be measured. Neuropsychological testing has been used to characterize the PTMD population and differentiate it from an idiopathic TMD group based on the results of cognitive and reaction time tests (Goldberg et al., 1996). There are few empirical data on the relation between neuropsychological deficit and response to medication, psychotherapy, and treatment setting. However, it was shown that baseline cognitive impairment may be an important predictor of treatment outcome. Recently, impairments in cognitive function have been shown to predict poor treatment outcome even in non-traumatic TMD patients and patients with somatic (ie non-orofacial) chronic pain condition, irritable bowel syndrome (IBS) (Grossi et al., 2001 in press).

(vi) Cognitive Deficits and Trauma

There is much debate on the nature and duration of cognitive deficits and post-concussive symptoms after mild head injury. It has been shown that subjects suffering a MHI performed less well on tests of divided and selective attention than patients without post-concussive symptoms and healthy controls six months after injury (Bohnen et al., 1992). From this it was concluded that cognitive deficits might be present up to 6 months after MHI when symptoms persist. It has been estimated that at least one-third of those with PTS do not recover, regardless of professional interventions (Kessler et al., 1995). A recent prospective study reported a rate of PTS, including PTH, of 34.4% at 1 month after the motor vehicle accident and 17.6% 9 months after the accident (Ursano et al., 1999). They also reported that the recovery rate slowed greatly after 6 months, with only 22.5% recovery between 6 and 12 months after the accident. This high rate of PTS 9 months after a MVA indicates the potential chronicity of serious MVA-related PTS. The findings indicate that patients with mild head injury and subjective symptoms may manifest demonstrable cognitive deficits.

A comparison of neuropsychological function of MVA victims diagnosed with PTS with those not diagnosed with PTS found no difference (Hickling et al., 1998). This study did however point out that a number of their subjects were involved in litigation which may have influenced patient responses. The assessment of neuropsychological functioning has become a common practice in the comprehensive evaluation of patients sustaining TBI. Frequently, diagnosis of mild TBI is based on neuropsychological test findings as the primary and most sensitive measure for "objective" documentation of such injuries. When specific, sensitive neuropsychological measures are employed,

headache pain is generally found to exert a significant and negative effect on neuropsychological test performance, at least for persons reporting persistent subjective complaints. Numerous studies have reported greater impairment in neuropsychological testing among patients suffering PTH following MVA injury (Gfeller et al., 1994; Gimse et al., 1997; Radanov et al., 1992 a and b). These tests varied but generally evaluated memory function, mental processing speed, divided attention and concentration as well as verbal associative fluency.

A large-scale study of 184 head injury patients (Tsushima and Tsushima, 1993) documented objective evidence of neurocognitive impairment but failed to find any significant relationship between the overall presence or frequency of headaches and neuropsychological functioning on the Luria-Nebraska Neuropsychological Battery (LNNB). However, it was unclear whether headaches were present at the time of test performance. In a study of 42 subjects with CPTH following MVAs, one group found that the 21 patients with the most frequent of 10 post concussion symptoms in the week prior to testing showed significantly greater impairment on 6 of 13 measures of neuropsychological functioning (Gfeller et al., 1994). More recently, a similar study found no statistically significant relationship between headache presence or intensity and neuropsychological test performance in a group of 125 patients seeking treatment for CPTH (Lake et al., 1999). It was suggested that these results supported the robust inter-subject reliability of standardized neuropsychological testing regardless of pain level in patients with CPTH resulting from mild head/neck injury.

Statement of the Problem

Pain is a complex multidimensional subjective experience modulated by emotion, attitude, and perception. In the literature, chronic pain is described as pain that persists 6 months after injury (Martelli et al., 1999). The longer pain persists, the more recalcitrant it becomes and the more treatment goals move toward "management" of pain and "coping" versus "cure" (Martelli et al., 1999). Chronic pain is a major health problem both in terms of the numbers of persons affected and in the cost to the economy. The potential role of smoking as a modulator of musculoskeletal pain has been studied with no absolute conclusions. As discussed earlier, there are data to support the notion that smoking can be either a mediator or risk factor for chronic or more severe pain or even a possible pain inhibitor. Given the controversial effect of smoking on treatment outcome and /or pain severity, I chose to focus on the association between smoking and pain severity/recovery in another craniofacial pain population, those with TMD.

Evidence supports the clinical impression that following a MHI; PTHs often persist indefinitely if they are not eliminated in the first 6 months after the accident (Ursano et al., 1999). Long-term, the most problematic consequences after a MHI often involves the individual's cognition, emotional function, and behavior. Despite the high numbers of MVAs and the epidemiological data that suggest relatively high numbers of accident victims suffer with PTH, there has been very little focus on early identification of non-responders to treatment. Being able to identify those patients most likely to respond poorly to therapy may help us to design more effective and focused treatment strategies. In return, this may lead to more predictable and positive treatment outcomes.

Objectives

To gather further insight into factors influencing TMD and treatment outcome, I propose to:

1) Determine the effects of smoking on the response to treatment of TMD symptoms using a general survey.

In light of the problems associated with MHI and the subsequent chronic PTH, the objectives of my study were:

1) To determine the presence of reduced cognitive AND/OR neuropsychological function in post-traumatic headache using appropriate neuropsychological tests in a PTH pain population.
2) Given putative reductions in cognitive or neuropsychological function in PTH, to determine whether such impairment can be used to predict poor treatment outcome for PTH both pre- and post-treatment.
3) To perform a preliminary, descriptive assessment of the prevalence of signs and symptoms of TMD in the PTH pain population in order to establish parameters for larger prevalence studies.

Hypotheses

On the premise that smoking has a negative impact on musculoskeletal pain I suggest the following hypothesis:

1) Non-smokers will respond better to treatment for TMD than current or past smokers.

From what is now known about the cognitive impairment of PTH sufferers and from previous studies within our research group evaluating the predictive ability of specific neuropsychological tests, the following hypotheses are proposed.

1) Poor neuropsychological test results are predictive of poor treatment outcome in a PTH pain population.

2) Patients with PTH pain will also demonstrate signs and symptoms of TMD.

Chapter Two

Materials and Methods

The study design has been divided into two parts. Part I is a survey of TMD patients, their smoking history and response to treatment. Part II is a prospective pilot study to evaluate several aspects of PTH and the response to treatment.

PART I

a) Survey Population

The group of subjects surveyed was identified from a chart review of patients seen at Mount Sinai Hospital for evaluation of possible temporomandibular disorder (TMD) (prior umbrella ethic approval obtained for a prior similar study). Eight hundred charts were reviewed and three hundred and thirty six subjects diagnosed with TMD were identified. A brief survey concerning their smoking history and treatment modalities was mailed to each of the 336 patients.

b) Survey Design

A simple checklist style survey (see Figure 1) was mailed to the 336 patients identified to have a diagnosis of TMD. Figure 1 is a copy of the questionnaire administered to these 336 patients via the mail. The survey inquired about treatment rendered for TMD, their smoking status and history as well as perceived response to treatment. A global transition outcome was utilized to evaluate treatment success, using the criteria of pain being the same, better or worse since treatment began. A self-addressed, stamped return envelope was included for ease of returning the survey and to increase the response rate. A short and simple checklist survey was employed for these same reasons. Two mailings were completed, the first to all 336 patients and the second

to those who did not respond to the first mailing. A letter was included with each survey, informing the patient of the purpose of the questionnaire and our desire to have them return it completed. One hundred and forty two surveys were returned for a response rate of 42.3%.

PART II

a) Patient Population

Patients who participated in this study did so voluntarily and signed a written consent form approved by the University of Toronto Internal Review Board. A total of 16 patients were acquired over a two-year period, from 1999 to 2001. Some subjects were obtained by referral after seeking treatment for headaches at the Wasser Pain Management Center at Mount Sinai Hospital. Others were solicited by advertisement in a local newspaper. All cases were newly diagnosed to avoid selection bias and to preclude previous history of extensive treatment measures, particularly pharmacologic agents that may interfere with cognitive abilities and hence the ability to complete the battery of tests. A total of 148 subjects were referred or responded to advertisements. After telephone screening, 22 were found to be suitable and able to participate. Each of these 22 subjects were further screened by one of two physicians (Dr. Allan Gordon or Dr. Jackie Gardner-Nix, at Mount Sinai Hospital) after which only 16 were selected as having fulfilled our criteria for selection.

b) Inclusion Criteria

The target population, based on clinical examination, included females aged 18 to 65 years old with the presence of headache as a primary complaint subsequent to a MVA. The primary complaint of headache had to be present for a minimum of 6 months

following the MVA with no overt pre-existing diagnosis of TMD and no symptoms of headache or TMD prior to the MVA.

c) Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

(1) The presence of a previously diagnosed psychiatric disorder (ie. depression)

(2) Patients with any type of metabolic, neoplastic, or vascular disorder (including migraine headaches) that could serve as other sources of head pain (Goldberg et al., 1996, Grossi et al,in press)

(3) Patients, upon presentation for the study who were currently on any type of prescribed medication or receiving treatment for their headache complaint

(4) Patients presenting with acknowledged or identified diagnosis of TMD

(5) The presence of dental caries or severe periodontal disease, which may be a source of facial pain.

d) Experimental design

This study was a case series, prospective pilot study to evaluate neuropsychological characteristics as predictors of PTH treatment outcome. In addition, the prevalence of TMD signs and symptoms was ascertained within this study group.

e) Treatment outcome measures

The effect of treatment was evaluated using a global transition outcome measure. Each subject was verbally asked the question, "Has your headache pain gotten better, stayed the same or gotten worse since you began treatment?" The responses were further subdivided with a better response suggesting successful treatment and responses of the same or worse grouped into treatment failure. This type of measure has limitations

because it is a subjective assessment only. Verbal scales are categorical, making it difficult to specify the size of each category and whether the categories are of equal spacing. In other words they are not very sensitive to changes in pain intensity. In anticipation of this we also included the visual analogue scale (VAS) to evaluate pain intensity at various time points during testing. The VAS has been successfully used in the past to measure changes in pain intensity (Dao et al., 1994; Freeman et al., 1998; Morin et al., 2000; Grossi et al, in press). The VAS used was a 100mm continuous scale with the extremes anchored in the following statements:

How Severe is your headache pain right now?

No Pain_____**Worst Pain Imaginable**

This question was asked to the patient prior to beginning the testing for the day and at the completion of all testing on the same day. In addition to asking about the pain intensity at a specific time point, I also asked how severe their headache pain was during the last month using a VAS. This would give me an indication of day-to-day headache severity as a comparison to their headache pain at the time of testing.

f) Improvement Criteria

At the end of treatment a minimum thirty percent reduction in pain compared to baseline, as measured using the VAS, was used as a criterion for improvement. This cut off point was selected based on previous findings that approximately seventy percent of patients who had a 30% or more reduction in pain at rest, as measured with the VAS (Dao et al., 1994), also agreed using global transition judgements that they were "better" (Grossi et al, in press).

g) Neuropsychological Tests

After screening by a physician and before commencing any treatment, each volunteer was seen for examination of the head and neck region followed by a series of neuropsychological tests. The tests selected for this study were based on previous findings that these tests are valuable measures to predict the response to treatment outcome (Goldberg et al., 1996; Grossi et al., in press), for PTMD, TMD and another somatic pain syndrome, irritable bowel syndrome (IBS). The tests utilized evaluated various aspects of cognition including speed and capacity of information processing, complex attention and learning, and memory, as follows:

(i) Simple and Complex Multiple-Choice Reaction Time Tests. Individuals who have suffered from a head injury may develop difficulties processing information. This deficit has been identified as an increase in reaction times to specific signals (Stuss et al., 1989).

In this investigation we utilized computer-based simple and complex multiple choice reaction time tests (SRT and MCRT). These tests were adapted from previous studies done within our research group (Goldberg et al., 1996, Grossi et al., in press), with minor changes to the computer program settings. Each subject completed a series of four reaction time tests, including one simple and three multiple-choice test (complex, with conflict and with constraint). Stimuli were white or colored on a constant background of dark gray and were displayed on a standard computer screen. The mean stimulus interval was 4 seconds with a 4 second delay. Subjects pressed a button in their preferred hand for SRT test while for the MCRT button both hands required responses.

Due to a computer error only data for the SRT and the MCRT with constraint were available for analysis.

In the SRT each subject had to respond to 50 stimuli and the response was measured in milliseconds. In the MCRT, the stimuli were either a target or a nontarget. Again, the computer randomly selected the stimuli. The target stimulus had a 40% probability of presentation and was randomly selected prior to test onset. The subject pressed the button in the preferred hand in response this target and the button in the other hand was for response to the non-target stimulus. In each case, 100 stimuli were presented.

(ii) California Verbal Learning Test (CVLT). The CVLT was designed to evaluate multiple cognitive parameters using an everyday verbal memory task (Delis et al., 1987). This test is a 16-item, four category shopping list that can be used to test a subject's immediate recall. The subject was presented with a "Monday" list of 16 items over five trials. Performance was evaluated with respect to semantic and serial learning strategies, retention of information over time, and free versus cued recall versus recognition memory. Published norms for females aged 17 to 44 years for the mean CVLT correct responses ranged from 62 to 64 (Delis et al., 1987).

(iii) Peterson – Peterson Consonant Trigram Test. Another test utilized to evaluate short-term retention and memory was the Peterson-Peterson Consonant Trigram Test. The purpose of this distractor test was to prevent rehearsal of material being held for short-term retention testing (Peterson & Peterson, 1959). The test measures the auditory short-term memory of three consonants under interference conditions. Five trials were given for each time interval (0, 3, 9 and 18 seconds). The outcome measured

was the number of total correct letters recalled at each of the three time intervals and the total possible score was 60.

(iv) The Symptom Checklist – 90 Revised. To evaluate the nature of psychological disturbance or distress, the Symptom Checklist-90 Revised (SCL-90R) test was administered. Derogatis and Cleary (1977) developed this 90-item self-report symptom inventory to identify the presence of psychological symptoms experienced by subjects during the 7 days prior to administration of the test. Each question is rated on a five-point scale of distress (e.g. 0 = no distress, 4 = extreme distress) and includes 9 primary symptom scales. Scores are expressed in terms of a t score, with a mean of 50. Evidence suggests that virtually all patients with chronic pain will have high scores with the SCL-90R. For this reason it was included in our series of neuropsychological tests. From the various scales we selected the depression scale and the revised head injury scale to analyze and compare. Comparisons were based on the raw scores.

(v) The Quality of Life Questionnaire (QLQ). The Quality of Life Questionnaire was developed to assess the quality of an individual's life across a broad range of specific areas. It is a 192 item, self report measure consisting of 15 content scales and a social desirability scale. In addition, the questionnaire yields an overall Quality of Life score. The QLQ may be useful as an evaluative measure of the impact of programs and changes in services upon individual life quality. As well, measuring quality of life is an important way to evaluate the effectiveness of individual therapy or drug therapy (Leu, 1985). The scores on the Profile Forms are reported as T-scores. After evaluating the QLQ, three categories, low, average and high, are usually sufficient to describe variations in T scores. Average scores are defined as falling between 40 and

60, while T scores of 39 or less indicate a low quality of life, whereas T-scores of 61 or above may suggest a high quality of life (Evans and Cope, 1989). At each testing session, each subject was asked to fill out a quality of life questionnaire. The raw score was then evaluated and compared.

h) Clinical examination

To determine the prevalence of signs and symptoms of TMD within our population, each subject entering this investigation underwent a complete extraoral and intraoral clinical examination by one examiner. The extraoral examination included palpation of the masseter, temporalis, sternocleidomastoid and medial pterygoid muscles, as well as palpation of the TMJ itself. Clinical examination also included assessment of maximum interincisal opening, assisted and unassisted, and evaluation of joint sounds including clicking, popping and crepitation. Intraorally, several muscles were also evaluated for tenderness and these included the medial pterygoid, coronoid attachment of the temporalis, lateral pterygoid and zygomatic attachment of the masseter.

The scoring of pain responses to muscle palpation and temporomandibular joint (TMJ) noises was adapted from the grading scale described previously (Grossi et al., in press). A grading scale of 0 to III was assigned for both muscle pain and TMJ sounds. These scores were then recoded into two groups, with a grade 0 or I being considered a negative score; and grades II or III being considered a positive score.

Other clinical measures included overbite and overjet along with intraoral assessment for the presence or absence of caries, periodontal disease and sensitivity to percussion. These last measurements were evaluated to rule out the presence of dental

sources of facial pain. Patients were also asked whether the clinical examination had exacerbated their headache pain.

Eleven of sixteen volunteers were tested at two separate time points. All sixteen underwent the tests already mentioned, prior to treatment. Eleven of these patients were tested a second time, six to twelve months after treatment began. This allowed for comparison of pre and post-treatment scores in relation to treatment outcome (success or failure). The five subjects who were not retested were called three to twelve months after treatment began and asked over the phone whether their headache pain had gotten better or worse, or stayed the same. These subjects refused to participate in the second test for various reasons, such as being unable to take time off work, or that it was a long distance to travel.

i) Treatment

Medical therapy was not limited in any way and encompassed all types of treatment modalities to allow for the best possible success. Physicians did not follow a specific protocol and treatment was provided based on each subject's needs. The variability in treatment provided is definitely a flaw in the study design but it is unethical to withhold treatment that may be of benefit to patients. Working with this understanding, the treatment provided differed for most patients, however many received some type of pharmacological intervention. Suffice it to say that any and all appropriate treatment approaches were rendered in order to effect improvement.

Statistical Analysis

All statistical analyses were completed using the SPSS statistical program. The survey response data were evaluated initially to compare the population of subjects who responded to the questionnaire to those who did not. The Chi-squared test was used to complete this task. The data were then weighted and variables such as smoking and treatment modality were compared to therapeutic outcome using the Chi-squared analysis as well. The predictability of cognitive testing for treatment outcome was evaluated using the independent t-test. Because the sample size was small, these values were compared to the non-parametric equivalent, the Mann-Whitney U test. The paired t-test was utilized to compare pre and post-treatment scores for the eleven subjects tested at two time-points. Again, this was compared to the non-parametric equivalent, the Wilcoxon-sign rank test.

Chapter Three

Results

Part I

A brief survey was mailed out to 336 patients diagnosed with TMD, and 142 people responded for a response rate of 42.3%. A comparison of the survey respondents and the non-respondents using Chi-squared analysis revealed no statistically significant differences with respect to gender, occupation, or marital status (see figures 2, 3 and 4). Figure 2 demonstrates the proportion of males and females that responded to the survey in comparison to those who did not. Note that there is no significant difference in the gender of respondents compared to non-respondents ($p>0.05$). Figure 3 illustrates a similar comparison between respondents and non-respondents with respect to occupation. This figure demonstrates that the number of respondents and non-respondents was similar for both skilled and unskilled workers ($p>0.05$). Figure 4 is another comparison of respondents and non-respondents, illustrating there was no significant difference in the response achieved for either the group of married or the group of not married subjects ($p>0.05$). When the age variable was dichotomized into two groups, 10 to 40 and 41 to 82, a significant difference was found ($p<0.05$), with the younger group responding less than the older age group (see figure 5). Figure 5 provides a comparison of the survey subjects based on their age and response status. It clearly illustrates that significantly fewer responses were obtained from the younger age group of subjects ($p<0.05$). Based on this finding, the data were then weighted and the remaining calculations were completed with the data weighted for age. Failure to do this would have been considered inappropriate from a statistical stand-point (Dr. D. Locker, personal communication).

The survey results indicated that 64.1% of respondents had never smoked (non-smokers), while 22.5% had smoked at some time and 13.4% were currently smokers (see figure 6). Figure 6 is a graphic representation of the proportion of the total number of respondents calculated to fall within each of the three smoking status categories, current smoker, former smoker and non-smoker. Approximately 13 fold more non-smokers were found among this TMD population than smokers. The number of smokers responding to the survey is similar to that expected based on reports that in 1998 24.1% of the population in the United States smoked (MMWR, 2000). Figure 7 demonstrates the percentage of respondents calculated to have received each of the six possible treatments listed on the survey. The most commonly prescribed treatment regimen for the respondents was found to be bite appliances with 52.8% having received this treatment (see figure 7). Also popular were medications and physiotherapy, with 35.2% and 33.1% of respondents receiving these therapies respectively (see figure 7). The survey respondents were 49.6% female and 50.4% male.

Chi-squared analysis of the weighted data revealed a statistically significant difference between smokers and non-smokers with respect to treatment outcome. Figure 8 provides a comparison of the smoking status as a function of treatment outcome. One and a half fold more non-smokers were better after treatment than current smokers ($p<0.05$) (see figure 8). Also, smokers reported their symptoms were worse more often than former smokers and non-smokers. Evaluation of the different treatment modalities and smoking status as a function of treatment outcome revealed that non-smokers were significantly better when treated with medications than smokers ($p<0.05$) (see figure 9), while no difference was detected when medication was not given (see figure 10). Figures

9 and 10 graphically compare the treatment outcome reported by survey respondents as a function of smoking status and the influence of medication. Figure 9 looks specifically at the influence of medication and demonstrates that non-smokers responded significantly better to medication than smokers ($p<0.05$). Figure 10 looks at the population that did not receive medication and shows that no difference in treatment outcome is reported between the smoking categories when medication was not prescribed ($p>0.05$). Figure 11 provides an illustration of the comparison of respondents not receiving physiotherapy on the basis of smoking status and treatment outcome. Similarly, figure 12 provides a comparison of respondents not receiving a bite appliance as part of their TMD therapy. Both figures indicate that more non-smokers not receiving physiotherapy or bite appliances reported their TMD symptoms to be better than current smokers ($p<0.05$) (see figures 11 and 12). A similar difference was not found when physiotherapy or bite appliances were prescribed; however, the p-value does approach significance for physiotherapy ($p=0.086$) (see figures 13 and 14). Figure 13 compares the respondents that did receive physiotherapy on the basis of their smoking status and reported treatment outcome. Note that smokers tended to improve more often than non-smokers when physiotherapy was prescribed, with the p-value approaching significance ($p=0.086$). This fact does appear to be anomalous but these patients did not receive only physiotherapy and there may have been other factors involved in treatment outcome. Moreover, given the number of statistical analyses and comparisons made in this study and the fact that significance was set at $p=0.05$, it is probable that some anomalous findings might surface (eg. false positives) Figure 14 outlines the proportion of respondents receiving a bite

appliance as part of therapy and indicates that smokers and non-smokers tended to respond equally well when a bite appliance was prescribed ($p>0.05$).

Other treatment modalities included surgical treatment, no treatment or some other type of treatment not included on the survey. Again, non-smokers not receiving surgical therapy reported their symptoms to be significantly better than current or former smokers ($p=0.021$). Very few respondents (fourteen in total) reported a history of surgical intervention and no significant difference was found between any of the smoking categories and a positive history of surgical treatment. No statistically significant difference was reported between groups for any other treatments not listed on the survey or for those not receiving any treatment at all. Chi-squared analysis of the number of therapies received indicated a statistically significant difference between smoking categories for those receiving one or fewer treatment modalities ($p=0.006$), with non-smokers responding better and with fewer treatments than current or former smokers. Those receiving two or more treatments did not show any significant difference between smokers or non-smokers ($p=0.123$).

Part II

Sixteen volunteers were tested for this study and after a 3 to 19 month treatment period, five reported improvement in their headache pain, nine were the same and 2 felt they were worse. Thus only about 30% of the PTH population actually improved with treatment. Eleven subjects were retested at an average time interval of 9.13 +/- 4.47 months of treatment. The initial testing sessions were on average 110 +/- 5.06 minutes in length. Clinical findings indicate the prevalence of TMD signs and symptoms was lower than expected in the PTH population. Based on the neuropsychological test outcomes

and the reported response to treatment, it was not possible to identify non-responders to therapeutic intervention with most tests. Only the MCRT test was found to be a predictor of treatment outcome, retrospectively. Table 1 provides a summary of the average test scores as a function of treatment outcome.

a) Neuropsychological Tests

(i) Quality of Life

Figure 15 is a graphic illustration of the pretreatment mean raw scores for the quality of life survey comparing those reportedly getting "better" with those who stayed the "same" or got "worse". The average quality of life score for those who were successfully treated did not differ significantly from those who were not treated successfully ($p>0.05$) (see figure15). The mean test score was 121.80 +/- 8.59 for those who responded well to treatment compared to a score of 100.73 +/- 4.47 for those who did not. Both groups had mean scores interpreted to be a high quality of life despite headaches. For the eleven volunteers tested at two time points, no significant difference was detected between scores pre and post treatment.

(ii) SCL-90R (Depression and Head Injury variables)

On the basis of the SCL-90R checklist, it was not possible to differentiate non-responders from responders. Figure 16 provides a summary of the pre-treatment mean raw scores for the SCL-90R checklist variables as a function of treatment outcome. Pre-treatment scores for both the depression and head injury groupings were not significantly different on the basis of the global transition outcome measure of, the same, better or worse ($p>0.05$). Figure 16 does however demonstrate an obvious trend, with the responders scoring lower (ie. better result) initially than non-responders. Figure 17

illustrates the difference in pre and post-treatment mean raw scores for the same SCL-90R variables for the eleven subjects retested. Note that the pre and post-treatment mean raw scores revealed no significant difference ($p>0.05$) (see figure 17).

(iii) Simple and Complex Multiple-Choice Reaction-Time Tests

Figure 18 provides a summary of the pre-treatment reaction times, in milliseconds, for the SRT target stimuli and the MCRT target and non-target stimuli, for the outcome measures of "better" and "same/worse". Reaction times to simple stimuli were not significantly slower in the group of responders than in the non-responders ($p>0.05$) (see figure 18). This finding was replicated for the complex tasks with constraint for the non-target stimuli but differed for the target stimuli, where a significant difference was found between the two groups ($p<0.05$) (Figure 18). The assessment of pre and post-treatment reaction times demonstrated no significant difference between pre & post-treatment test scores for the eleven volunteers retested.

(iv) Peterson-Peterson Consonant Trigram Test

The scores for the Peterson-Peterson Consonant Trigram Test were based on the total number of correct letter responses, regardless of the initial order of presentation (Peterson & Peterson, 1959). A mean pre-treatment score of 45.40 +/- 3.44 was demonstrated in the group of patients who reported their headaches were better, while the score for those not improving was 37.36 +/- 2.00 ($p>0.05$). A standardized mean score of 47.9 +/- 4.9 is considered to be within normal limits (Stuss et al., 1985). Fifteen of sixteen subjects had scores less than the 47.9 +/- 4.9 at the initial testing appointment. Figure 19 compares the mean raw scores for the Peterson-Peterson Consonant Trigram

test pre and post-treatment. The pre-treatment mean for the eleven retested patients was not significantly different from the post-treatment mean score ($p>0.05$) (see figure 19).

(v) California Verbal Learning Test

Immediate recall of the shopping list was not significantly better for those responding well to treatment compared to those not responding well ($p>0.05$) (see Table 1). Figure 20 compares the presence of clustering, intrusions and perseverations in the pre-treatment scores for those subjects getting "better" and those remaining the "same" or getting "worse". Information processing as demonstrated by clustering of similar items was similar in both groups, and there was also no statistically significant difference in the level of intrusion of new words into the list ($p>0.05$) (see figure 20). Figure 19 (already mentioned earlier) compares the pre and post-treatment immediate recall mean raw scores determined using the California Verbal Learning test. Immediate recall scores pre and post-treatment for the eleven subjects retested was not significantly different ($p>0.05$) (see figure 19).

b) Clinical Examination

Clinical examination demonstrated that 56% of subjects had one or more signs of TMD (see Table 1). Pre-treatment findings revealed that three non-responders and one responder demonstrated TMJ noises upon opening and closing. Only the masseter and medial pterygoid muscles had any grade II-III pain reaction on palpation extra orally. Intra orally, the medial pterygoid, lateral pterygoid, coronoid attachment to the temporalis and the zygomatic muscles all had at least one site with grade II-III pain reaction on palpation in the non-responding group of patients (see Table 2).

c) Visual Analogue Scale for Pain

Pain scores based on the VAS revealed a statistically significant difference between the worst pain experienced prior to treatment and the worst pain experienced after treatment for the eleven subjects retested ($p= 0.021$) (see Table 4). An average VAS pain score at the initial testing session was 93.45 +/- 2.19 compared to 75 +/- 9.32 after treatment. Two of the eleven retested subjects had a reduction in pain score greater than 30% based on the VAS. These two subjects both reported their headaches were better on the global transition outcome measure as well. Those subjects that did not report a positive treatment outcome ("better") had correspondingly low reductions in their VAS scores. None had a greater than 30% reduction in their worst pain VAS scores. Of the responders who reported they were "better" and were retested, the mean reduction in VAS was 75 mm. Measures of initial pain at each testing session and pain after testing approached statistical significance but were in fact not significant (see Table 4).

Figure 1: Questionnaire sent to patients identified to have temporomandibular disorder diagnosis.

Please check off the response that applies to you for each question:

What is your smoking history?

- ❑ Current smoker
- ❑ Quit smoking within last year
- ❑ Quit smoking over a year ago
- ❑ Never smoked

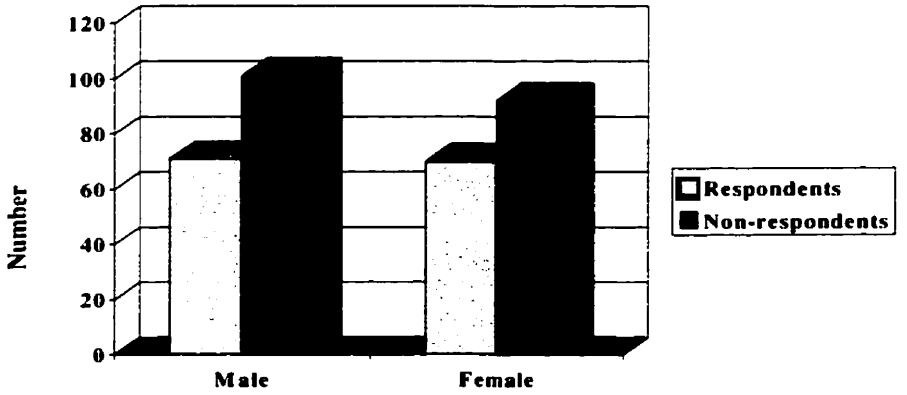
What treatment have you had for your temporomandibular joint pain to date? (check all that apply)

- ❑ Medication
- ■ Physiotherapy
- ❑ Bite appliance
- ❑ Surgery
- ❑ Other (please list)_____

How are your temporomandibular joint symptoms since you started treatment?

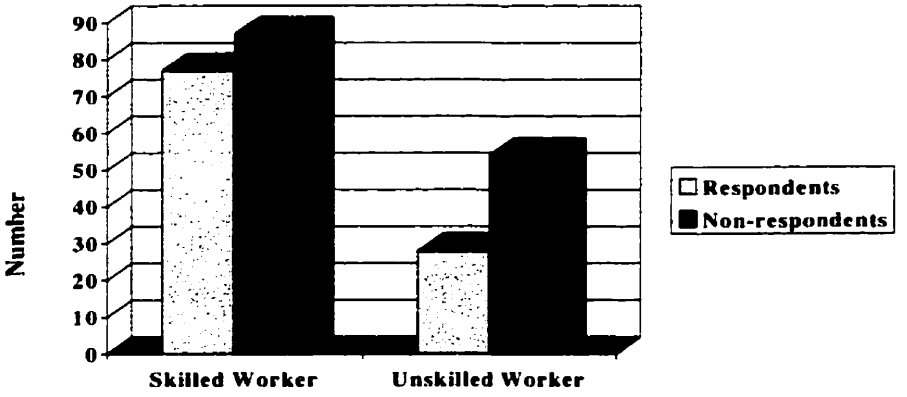
- ❑ Same
- ❑ Better
- ❑ Worse

Figure 2: Comparison of the number (N) of survey respondents to non-respondents on the basis of gender



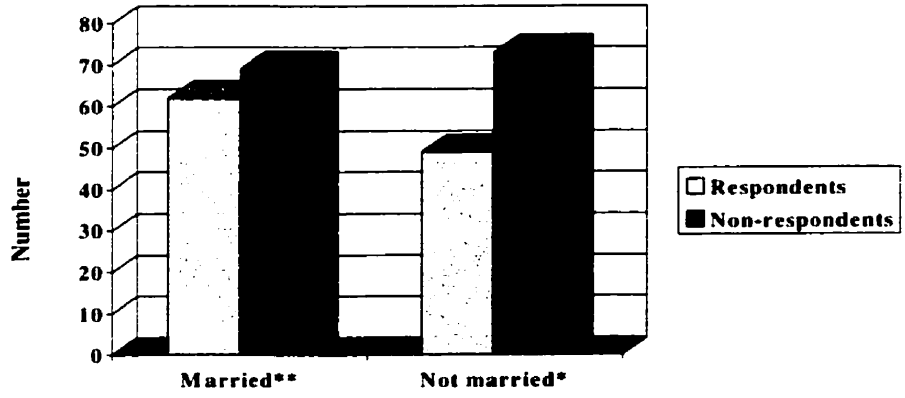
p=0.721 based on a Chi-squared analysis showing no difference between gender for respondents vs non-respondents.

Figure 3: Comparison of the number (N) of survey respondents and non-respondents on the basis of occupation.



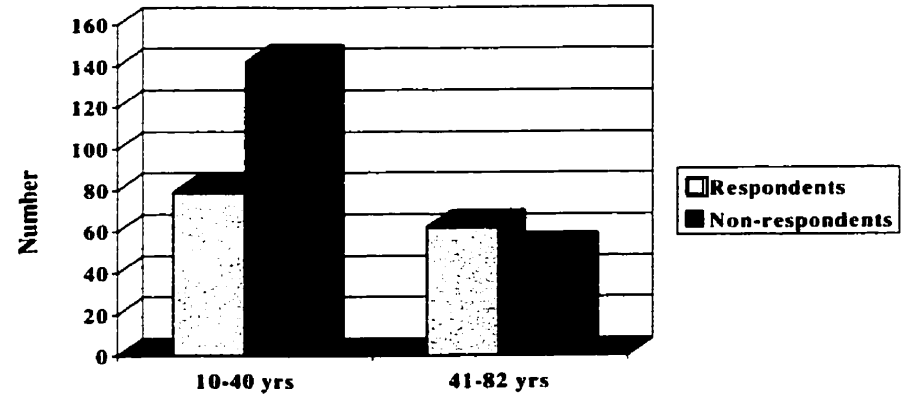
p=0.056 which is approaching statistical significance for skilled vs unskilled workers and response status.

Figure 4: Comparison of the number (N) of survey respondents based on their marital status (*refers to single, divorced, separated or widowed; **refers to married or common law).



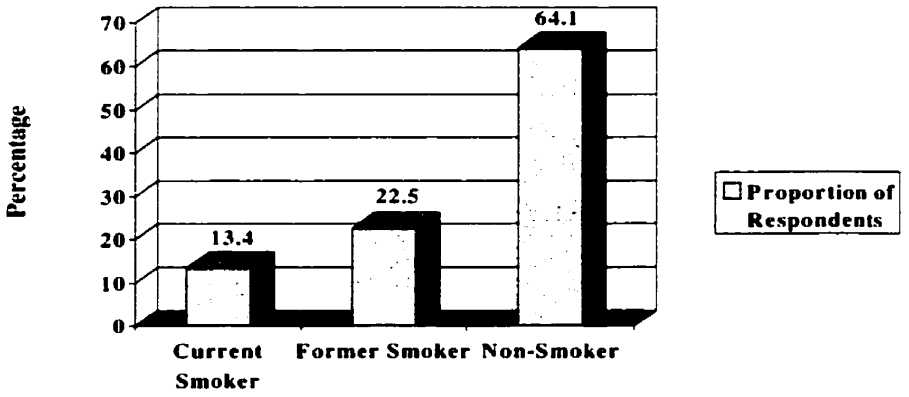
p=0.251 based on Chi-squared analysis showing no difference in response rates based on occupation

Figure 5: Comparison of the number (N) of survey respondents and non-respondents on the basis of age.



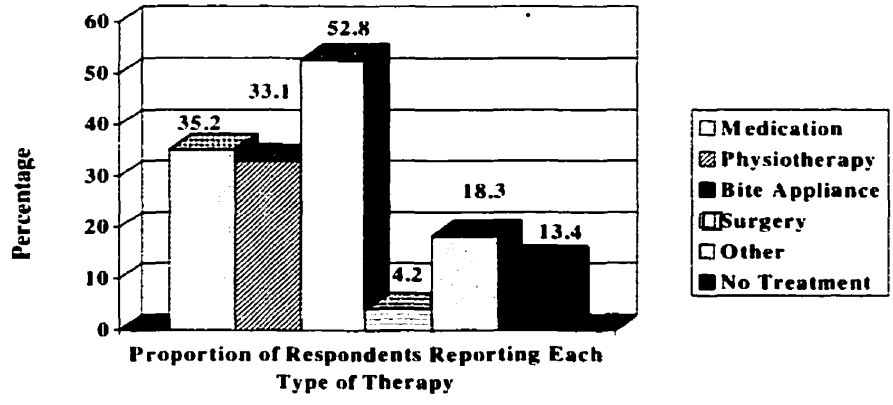
p<0.05 and therefore a statistically significant difference is reported for response between these age groups.

Figure 6: Smoking status of survey respondents, presented as a proportion of the total number of respondents (N=142).



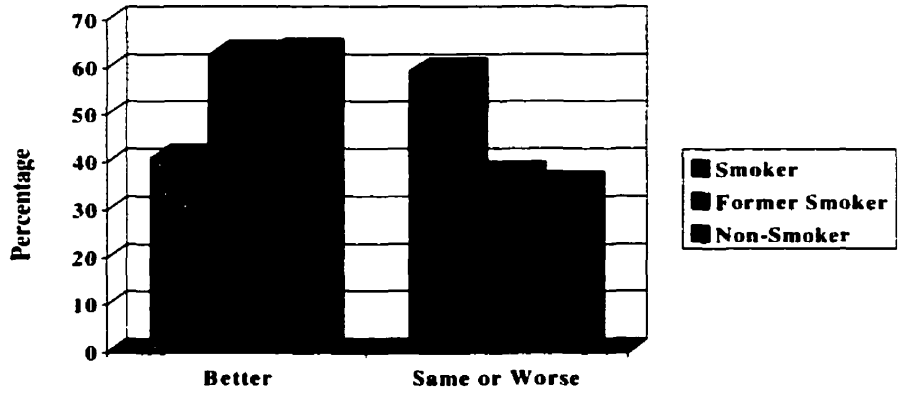
Values in the bars represent actual percentages.

Figure 7: Proportion of respondents reportedly receiving each of the different types of therapy listed on a brief survey.



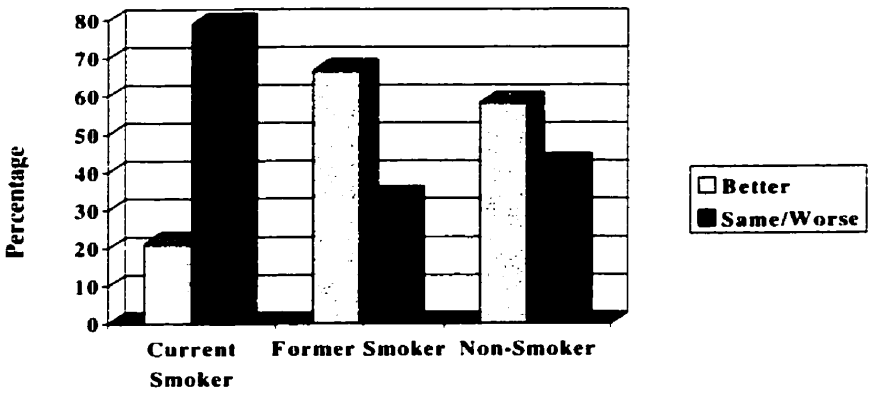
Values within bars represent actual percentage of respondents receiving the given therapy.

Figure 8: Treatment outcome (reported as a percentage) as a function of smoking status, with former smokers having quit more than one year ago (the data has been weighted).



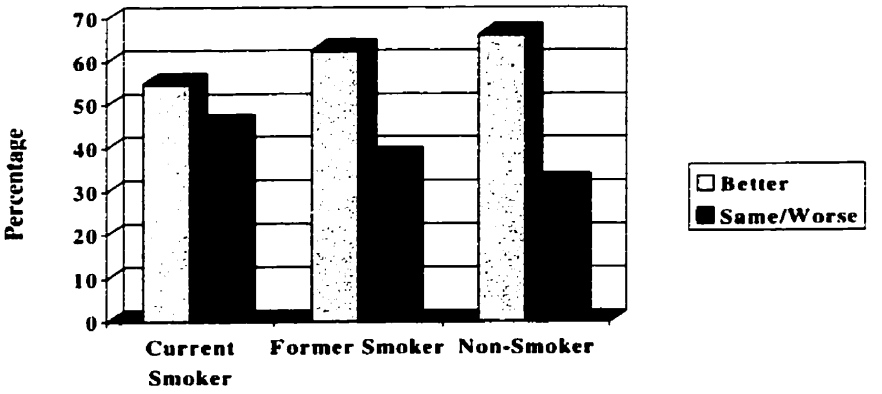
$p<0.05$ using a Chi-squared analysis showing that smokers reported their symptoms as being the same or worse more often than former smokers and non-smokers, with the later groups reporting similar results.

Figure 9: The percentage of respondents who reported receiving medications presented as a function of smoking status and treatment outcome.



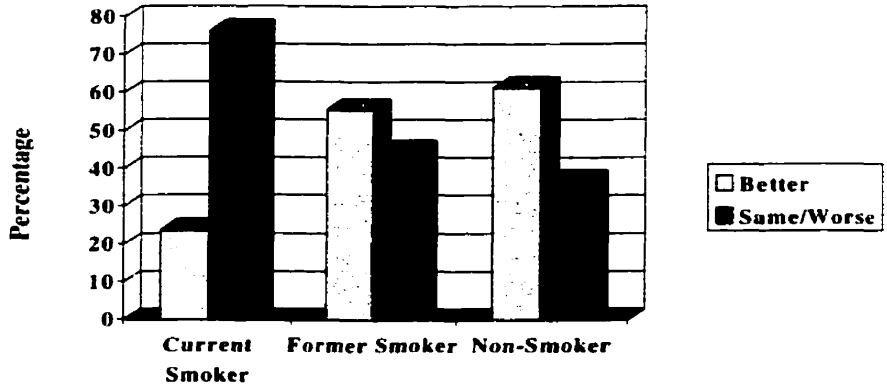
p<0.05 using Chi-squared analysis showing that smokers tended to respond to medications less favorably than former smokers or non-smokers.

Figure 10: The percentage of respondents reportedly not receiving medications presented as a function of smoking status and treatment outcome.



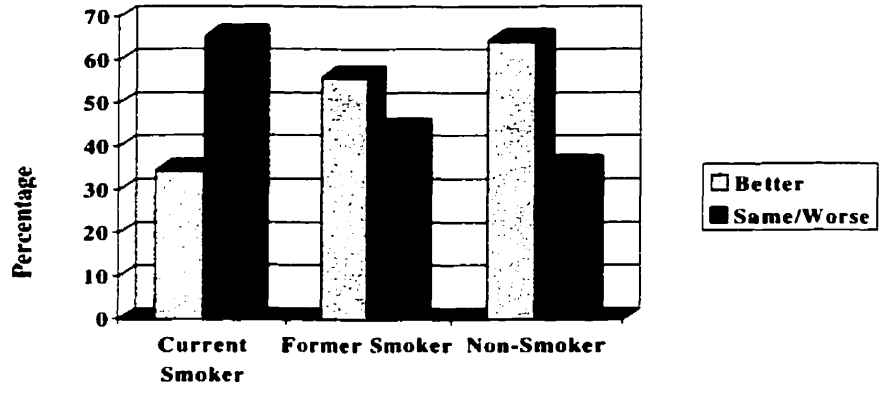
p=0.451 using Chi-squared analysis showing that smokers responded similarly to receiving no medications when compared to former smokers and non-smokers.

Figure 11: The percentage of respondents not receiving physiotherapy presented as a function of smoking status and treatment outcome.



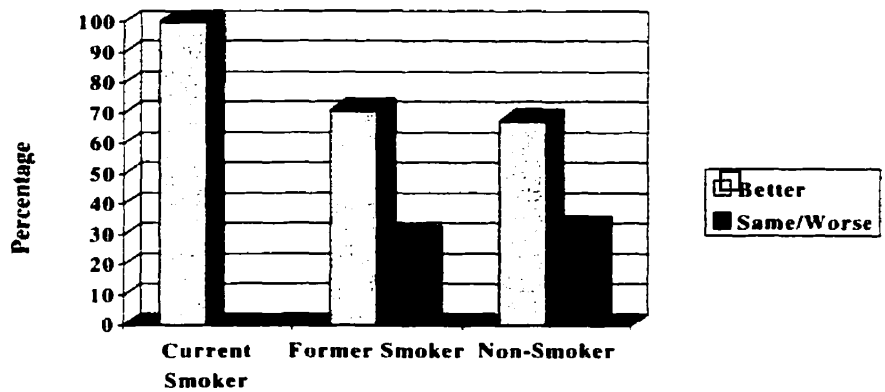
p<0.05 using Chi-squared analysis showing current smokers tended to be the same or worse more often than former smokers or non-smokers.

Figure 12: The percentage of respondents not receiving a bite appliance presented as a function of smoking status and treatment outcome.



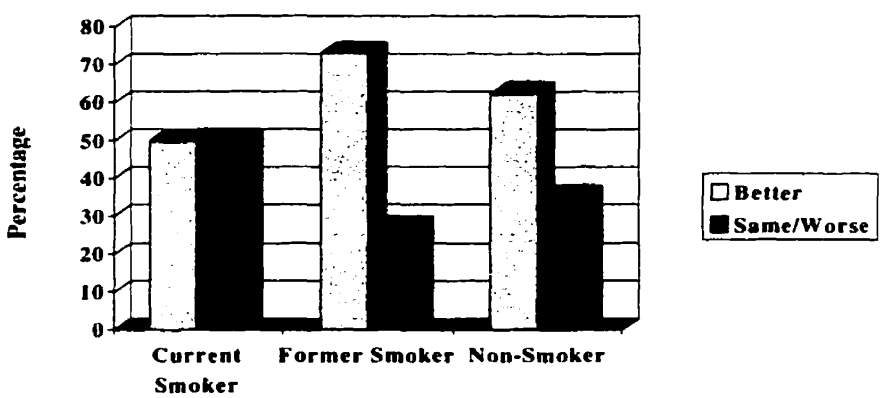
p<0.05 using Chi-squared analysis showing smokers not receiving bite appliances were more likely to be the same or worse than former smokers and non-smokers.

Figure 13: The percentage of respondents reportedly receiving physiotherapy presented as a function of smoking status and treatment outcome.



p=0.086 using Chi-Squared analysis showing smokers responded just as well to physiotherapy as former smokers or non-smokers.

Figure 14: The percentage of respondents receiving a bite appliance presented as a function of smoking status and treatment outcome.



p=0.450 using Chi-squared analysis showing smokers responded just as well to bite appliance therapy as former smokers and non-smokers.

Table 1: Response to treatment as a function of baseline scores.

Baseline variable	Response to treatment (mean±std error)		Significance*
	Better (n=5)	Same or worse (n=11)	
Quality of life	121.80 ± 8.59	100.73 ± 4.47	p = 0.610
SCL Depression	0.862 ± 0.267	1.354 ± 0.247	p = 0.234
SCL Head injury	1.438 ± 0.362	2.041 ± 0.191	p = 0.112
SRT	438.66 ± 52.00	553.69 ± 84.06	p = 0.610
MCRT (target)	436.66 ± 43.85	624.90 ± 79.99	**p = 0.047***
MCRT (nontarget)	446.80 ± 36.56	576.52 ± 76.21	p = 0.336
Trigram	43.40 ± 3.444	37.36 ± 1.997	p = 0.140
CVL score	57.00 ± 2.49	54.73 ± 2.625	p = 0.775

***p values reported from Mann-Whitney U Test**

Table 2: *Identification of the Prevalence of Muscle Groups With Grade II-III (Moderate/Severe) Pain on Palpation*

Muscle site (left and right)	Pre-treatment (n=32 sites)	Post-treatment (n=22sites)
TMJ noise	12.5% (4)*	31.8% (7)
Masseter (external)	6.25% (2)	0% (0)
Temporalis(external)	0% (0)	0% (0)
SCM (external)	0% (0)	0% (0)
Medial pterygoid (external)	6.25% (2)	9.0% (2)
Medial pterygoid (internal)	9.37% (3)	4.54% (1)
Lateral pterygoid (internal)	3.12% (1)	9.0% (2)
Coronoid insertion (internal)	25.0% (8)	31.8% (7)
Zygomatic insertion (internal)	9.37% (3)	0% (1)
Opening < 35 mm (interincisal)	18.75% (3)	27.2% (3)

*The number of sites within each category is noted in parentheses.

Table 3: Identification of the Pre-Treatment Prevalence of Muscle Groups With Grade II-III (Moderate/Severe) Pain on Palpation based on the Response to Treatment

Muscle site (left and right)	Better (n=10 sites)	Same or Worse (n=22 sites)
TMJ noise	0.1% (1)*	13.6% (3)
Masseter (external)	0% (2)	4.5% (1)
Temporalis(external)	0% (0)	0% (0)
SCM (external)	0% (0)	0% (0)
Medial pterygoid (external)	0.1% (1)	0% (0)
Medial pterygoid (internal)	0.1% (1)	9.0% (2)
Lateral pterygoid (internal)	0% (0)	4.5% (1)
Coronoid insertion (internal)	0.1% (1)	13.6% (3)
Zygomatic insertion (internal)	0% (0)	4.5% (1)

*The number of sites within each category is noted in parentheses.

Table 4: Pain Measurements ± Standard Errors of the Mean (Pre and Post Treatment) Based on a Visual Analogue Scale From 0 to 100 mm (n=11).

Pain	Pre-Treatment (mm)	Post-Treatment (mm)	Significance*
Initial	52.27 ± 7.64	42.36 ± 9.75	p = 0.066
Worst Ever	93.45 ± 2.19	75.00 ± 9.32	p = 0.021
After Session	64.45 ± 9.27	54.27 ± 10.89	p = 0.083

* p-value reported based on the Wilcoxon Signed Rank Test

Table 5: A list of possible therapies prescribed for PTH pain patients.

Possible Treatment Measures
1. Medications (ie. tricyclic antidepressants, Neurontin)
2. Physiotherapy
3. TMJ Evaluation with possible bite appliance
4. Acupuncture
5. Psychotherapy

*data regarding individual treatment modality used per patient were not available

Figure 15: Pretreatment quality of life mean raw score as a function of treatment outcome (n=16)

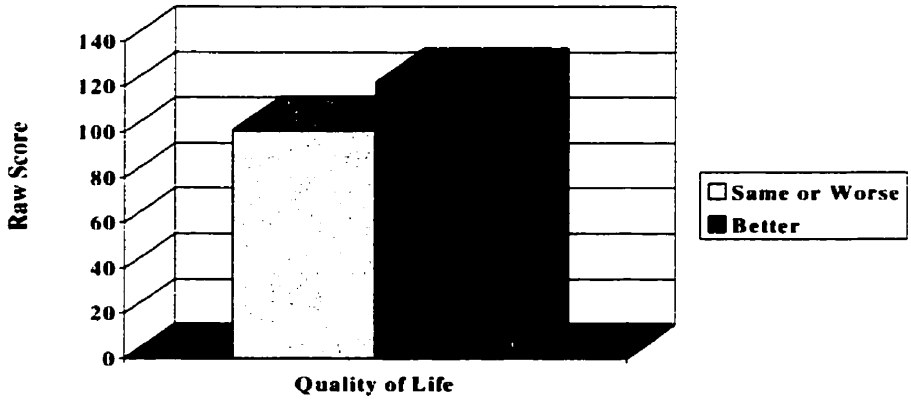


Figure 16: Pre-treatment mean raw scores for isolated questions from the Symptom Checklist-90R as a function of treatment outcome (n=16).

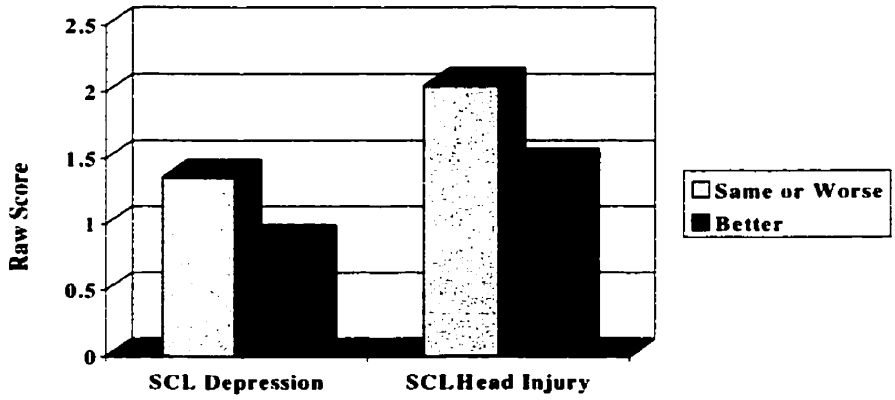
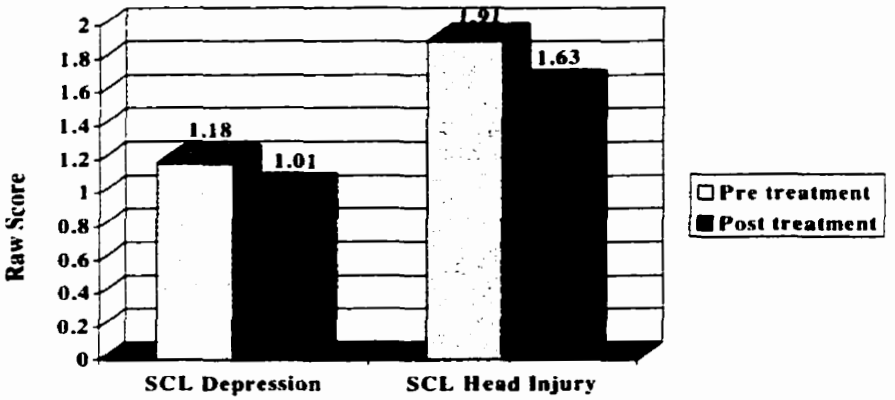


Figure 17: Mean raw scores for isolated questions from the Symptom Checklist-90R Pre and Post treatment (n=11)



p>0.05 for pre and post-treatment comparison of raw scores utilizing the Wilcoxon Sign Rank Test.

Figure 18: Pre-treatment mean reaction time to simple and complex multiple choice reaction-time stimuli, in milliseconds, as a function of treatment outcome (n=16)

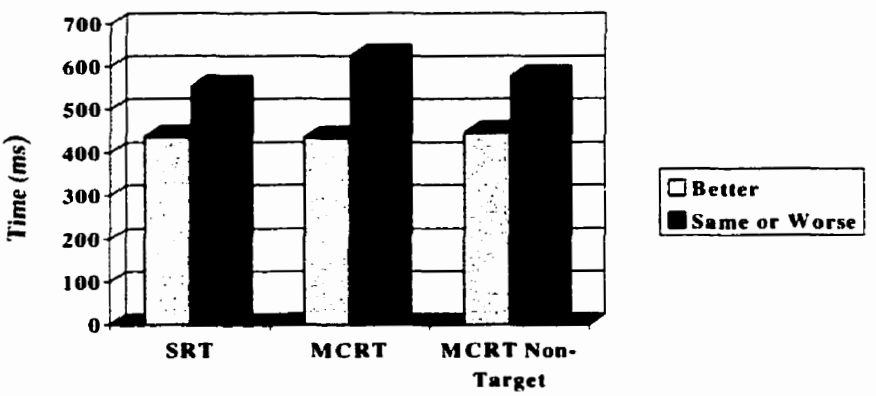
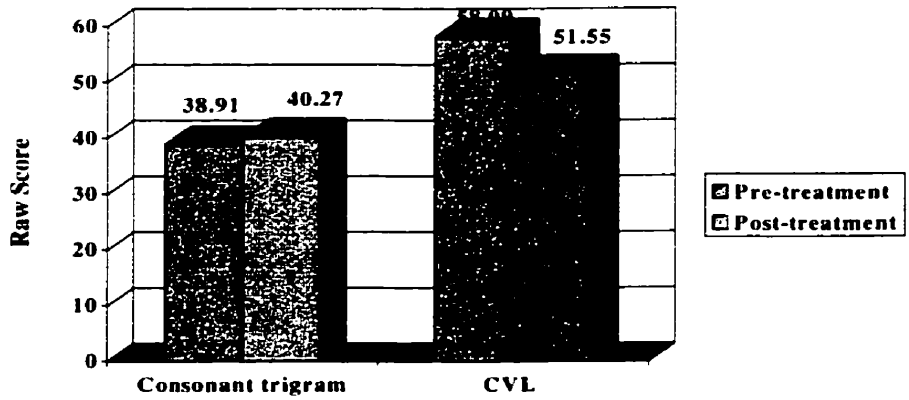
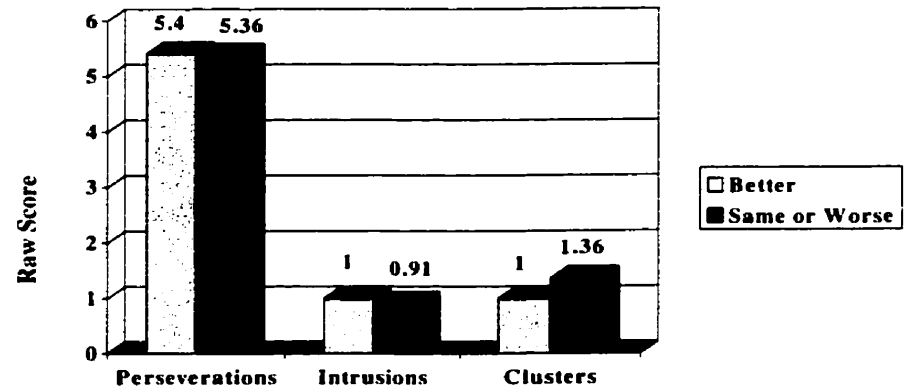


Figure 19: Mean raw scores for the Consonant Trigram and California Verbal Learning tests (n=11)



p>0.05 for pre and post-treatment comparison of raw scores utilizing the Wilcoxon Sign Rank Test.

Figure 20: California Verbal Learning Test demonstrating mean raw scores for perseverations, intrusions and clustering.



Statistical significance determined by Mann Whitney U test (p>0.05).

Chapter Four

Discussion

Smoking and TMD

On the basis of the data presented here, it appears that smokers respond less favorably to treatment than non-smokers. This outcome supports the theory that smoking increases pain and pain reporting (Brage & Bjerkedal, 1996). The exact mechanism by which this is achieved is still debatable but evidence in the literature suggests that polycyclic aromatic hydrocarbons can induce the release of cytokines causing subsequent inflammation and pain. Aryl hydrocarbon receptors are found within the cytosol of certain types of cells and binding of AhR ligands may up-regulate the production of inflammatory cytokines. Studies have shown that neuroendocrine peptides such as serotonin (5-HT) are present in association with hyperalgesia of the TMJ (Alstergren & Kopp, 1997) and in painful muscles (Kopp, 2001). Cytokines, such as IL-1b and TNF-alpha, have also been found in arthritic TMJs in association with hyperalgesia but they have not been identified in healthy joints (Alstergren et al., 1999; Nordahl et al., 2000). Similarly, prostaglandin E_2 (PGE_2) has also been detected in the arthritic TMJ (Alstergren & Kopp, 2000). There is an abundance of evidence to suggest the presence of inflammatory mediators within the TMJ at times of pain. Perhaps these mediators are upregulated by AhR ligands, such as those identified in cigarette smoke (eg. BaP, DMBA). Comparison of levels of these mediators in a smoking and non-smoking TMD population may help us to better understand this dilemma.

There may also be a central effect for the pain associated with smoking given the fact that it is now known that AhRs are found in many cells within the central nervous

system (CNS) (Preliminary observations in our laboratory based on the immunostaining for the AhR in brain). It has also been reported in reviews that many neuropeptides such as substance P and calcitonin gene-related peptide are localized in the trigeminal or dorsal root ganglia of nociceptors (Tenenbaum et al., in press). The release of these peptides may contribute to central modulation of noxious stimuli and perhaps to peripheral neurogenic inflammation and sensitization.

Another finding within this TMD population was that medication was more beneficial for non-smokers than smokers. Perhaps this fact is due to the increased inflammation produced by the presence of BaP and DMBA in cigarette smoke. If the AhR ligand theory holds true, then smokers may have higher levels of pro-inflammatory mediators in their muscles or joints than non-smokers. Although medications were not listed in detail, we know from initial survey of this population that many subjects received anti-inflammatories as part of their pharmacological intervention. It may be that the excess inflammatory mediators induced by smoking is too much for anti-inflammatory medications, at typical dosages, to reduce. Another significant finding was that non-smokers responded better even with fewer treatments than smokers or former smokers. This indicates that non-smokers receiving limited treatment or no treatment will do better than smokers. I was unable to show the same thing for the category of two or more treatment modalities. Again, linking this to smoking status suggests that the presence of aromatic hydrocarbons in the body interferes with healing in the absence of treatment or with limited treatment. For all comparisons of treatment outcome and smoking status, former smokers lie between current and non-smokers for the number of subjects reportedly getting "better". It is also known that AhR ligands have a long half-

life compared to nicotine. Based on the treatment outcome differences reported for non-smokers and former smokers, it is possible that the lingering presence of AhR ligands within the body continues to mediate pain. This finding further supports the notion that AhR ligands are the main factor influencing pain and not nicotine.

Subjects were chosen to receive the survey based on a diagnosis of TMD using their charts as a source for identification. The questionnaire distributed was brief to achieve a high response rate but as a result presents a number of limitations. The severity of TMD pain was not queried, nor was there any measure of the extent of smoking. A good prospective study looking at nicotine levels as a reflection of the level of smoking an individual is doing would help to resolve this concern. As well, I did not inquire about specific medications, types of bite appliances or the length of treatment period. A more detailed survey would have allowed for a more sophisticated statistical analysis of the TMD population. Despite all of this however, I was still able to show that smoking does influence treatment outcome negatively and this may provide a stepping stone to further prospective research in the area of TMD and smoking. For example, if the assumption is correct that AhR ligands and not nicotine are the major factors mediating chronic musculoskeletal pain in smokers, then AhR antagonists such as resveratrol (Singh et al., 2000; Gentilli et al., 2001) might be used as adjuncts to treatment in smoking TMD patients. While resveratrol is also a cox-2 antagonist, if it did work, it would probably not be because of cox-2 antagonism, given the minimal benefit of non-steroidal anti-inflammatories in our smoking TMD population.

It is important to understand that, along with BaP and DMBA, there are thousands of contaminants in cigarette smoke, and that any of the components of smoke may play a

role, either alone or in combination, in the mediation of chronic musculoskeletal pain. Another consideration is that although smoking was associated with non-response to treatment, perhaps this is due to some analgesic property of cigarette smoke or some characteristic of smoking or smokers that is independent of smoke.

To my knowledge there have been no studies specifically evaluating the relationship between smoking and TMD. Studies focusing on chronic musculoskeletal pain and the role of cigarette smoke have not included the TMJ as a site for consideration (Andersson et al., 1998). It has been suggested that TMDs may be responsible for a substantial amount of oro-facial pain (Romanelli et al., 1992) and given this fact, factors influencing the treatment of TMDs need to be better understood, including the effect of smoking.

Post-traumatic Headaches

a) Neuropsychological Tests

The neuropsychological function tests selected for this study were unable to statistically predict treatment outcome. Only the MCRT with constraint, target stimuli, was found to identify responders from non-responders. Other test results were not significant but did at least demonstrate trends suggestive that they may have been predictive had a larger population been tested. It was also very clear that a small proportion of subjects responded well to treatment, and reported feeling "better" (30%). This confirms previous findings by other groups that PTHs are often persistent and difficult to treat beyond 6 months (Ursano et al., 1999). All the subjects within this study had suffered with PTH for a minimum of 6 months.

In general, most of the PTH suffers were found to have impaired neuropsychological test scores. Fifteen of the sixteen subjects had Peterson-Peterson Consonant Trigram test scores lower than the standardized mean scores. Similarly, the average CVL test scores were below the published norms. The raw scores for the SCL-90R checklist were very similar to previous findings for a post-traumatic TMD population also found to have neuropsychological deficits (Goldberg et al., 1996). Overall, the PTH pain population for this study did demonstrate cognitive impairment, but this impairment was not significantly different among those who responded to treatment and those who did not. Contrary to what was expected, responders and non-responders were found to have quality of life scores in the high range. This indicates that despite their chronic pain, all subjects felt they had a good quality of life.

As previously mentioned, neuropsychological testing has been used to characterize the PTMD population and differentiate it from an idiopathic TMD group based on the results of cognitive and reaction time tests (Goldberg et al., 1996). As well, they have been able to predict poor treatment outcome in non-traumatic TMD patients and patients with IBS (Grossi et al., 2001 in press). Contrary to expectations, the same neuropsychological tests were unable to predict treatment outcome in a PTH pain population. The explanation for this may be very simple and reflect the small sample size obtained or it may be related to fundamental differences in subjects with PTH versus PTMD. Perhaps the origin of the pain is important and TMD pain is often musculoligamentous or articular in origin while PTH pain is not. However, as pointed out in reviews, increased levels of pro-inflammatory mediators have been found in both muscles and joints (Kopp, 2001). The population selected for this study had also not

been treated before which may be an indication of the degree of pain experienced to begin with. It is possible that those seeking treatment early have more serious injury, pain and subsequently cognitive deficits. Age may also be a factor in cognitive testing. The age of subjects in other studies evaluating neuropsychologic tests (Goldberg et al., 1996; Grossi et al., 2001 in press) have not been reported but in this study population, younger subjects tended to score better than women in their forties or older (based on general impression, no data available). Preliminary data from the pain group at Mount Sinai Hospital suggests that patients presenting to the Wasser Pain Management Centre tend to be older than the average TMD patient. Therefore, perhaps due to age differences, cognitive tests are better at predicting treatment outcome in younger groups. Unfortunately the exact influence of age cannot be evaluated in this study but future studies should compare cognition among different age groups and the predictability of neuropsychological testing. In spite of all these possibilities and given the trends exhibited by the test scores among this study population, I suspect that a larger sample size for a PTH pain population would serve to achieve a statistically significant difference between responders and non-responders to treatment.

b) Clinical Examination

The clinical examination findings demonstrated that most subjects had at least one muscle site with a positive response to palpation or one joint with a positive response for noise. However, the presence of one or two positive responses does not indicate a diagnosis of RDC/TMD (Dworkin & LeResche, 1992), meaning most subjects did not have TMD. Therefore, in general, the signs and symptoms of TMD within this PTH pain population were much lower than expected. Studies evaluating the frequency of TMD

signs and symptoms following a MVA have found muscle tenderness ranging from 38% of sites to 69%, depending on the muscle location (Goldberg et al., 1996). This is compared to a range of 0 to 25% found among this PTH population following a MVA. This finding is in agreement however with others that have shown no signs of TMJ clicking immediately after a MVA with evidence of cervical spine injury (Heise et al., 1992). Similarly, a retrospective study of records from the Victoria (Australia) Transport Accident Commission identified subjects involved in an MVA in 1987 and found TMD associated with 28 of 20,673 reported MVAs (Probert et al., 1994). These studies do not however focus on victims with PTH as a result of the accident.

c) Treatment

The treatment protocol for this study was not a specific regimen but rather was variable depending upon the treating physician and patient needs (see table 5 for possible treatment measures). This aspect of the study is a design flaw but unavoidable for ethical reasons. Most subjects did receive pharmacological intervention. I recognize that I have not indicated specific treatment rendered on a patient-by-patient basis. However, no one treatment modality has been shown to be superior to another. This is exemplified further by a recent study where it was shown that treatment outcome did not vary between caregivers and yet the caregivers did not follow standardized treatment regimens (Grossi et al., in press). Hence, I did not emphasize or attempt to differentiate between all different treatment modalities on an individual patient basis. Treatment of a PTH pain population has proven to be very difficult. It is for this reason I was seeking to explore predictors of treatment outcome to allow for early identification of the group of non-responders. Early identification may serve to filter patients to the appropriate therapy.

Although I did not demonstrate a statistically significant difference in cognitive impairment there was a definite trend in this direction. Moreover, others have found (Stuss et al., 1985; Goldberg et al., 1996; Grossi et al., in press) statistically significant reductions in cognitive function in non-responsive patients. Hence, although further study is required in the PTH population, it might be suggested that cognitive behavioral therapy (CBT) could be a useful treatment modality for this pain population as it is in others (Toner et al., 1998; Mishra et al., 2000). Cognitive behavioral therapy may allow them to manage and perceive their pain in a different manner that will allow them to cope better. Cognitive behavioral therapy provides training in relaxation, controlling pain through distraction techniques, pleasant activity scheduling, cognitive restructuring, as well as social skills (Mishra et al., 2000). A meta-analysis of 51 research studies looked at the overall efficacy, substantive efficacy and relative efficacy of cognitive coping strategies in influencing self-reported pain (Fernandez & Turk, 1989). Results showed 85% of the investigations had a positive outcome in increasing pain tolerance, increasing pain threshold or decreasing pain ratings compared to a no-treatment condition. Others have demonstrated the effectiveness of cognitive-behavioral skills training with TMD patients (Stam et al., 1984; Flor & Birbaumer, 1993; Mishra et al., 2000) and irritable bowel syndrome (Toner et al., 1998; Boyce et al., 2000). Thus, in light of the presence of cognitive impairments in this population, despite the fact that these impairments did not predict treatment outcome, and since pharmacological treatment was only modestly effective, CBT use should be evaluated for the PTH population.

Conclusions

As a result of this investigation relating to factors affecting treatment outcome in patients suffering from craniofacial pain, I was able to make the following conclusions:

Smoking & TMD

1. In smoker, smoking appears to be negatively associated with the response to treatment in a TMD pain population.
2. This could be related to AhR ligands, nicotine or any number of other components in smoke, none of which were investigated in this study. Therefore future prospective and interventional trials using AhR ligand antagonists like resveratrol are required.

PTH

1. Cognitive impairment is evident in virtually all subjects suffering with PTH.
2. Neuropsychological tests are not predictive or only mildly so, even with larger sample sizes of treatment outcome. Thus, larger prospective studies are required to confirm this.
3. Signs and symptoms of TMD are not common among this PTH population.

The sample sizes for the survey and the PTH pain study were both small but do provide a starting point for future research in these areas. In particular, the role of cigarette smoke and the influence of AhR ligands on the treatment of chronic pain needs to be addressed. In the PTH pain population it is important to recognize that the presence of cognitive impairment does not constitute evidence of a causal link between neuropsychological deficits and the clinical characteristics of PTH, but only co-morbidity. These findings illustrate the need to approach treatment of PTH pain more

broadly, to achieve higher success rates and to focus on newer treatment modalities such as CBT.

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