Multidisciplinary management and psychological functioning in orofacial pain

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Multidisciplinary management and psychological functioning in orofacial pain

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Abstract

Introduction: Pain is an unpleasant experience with both sensory and emotional components. Its management is complex due to various factors involved in pain perception by individuals. This is explored in my thesis in three stages. Firstly, a systematic review was carried out to explore the impact of psychological factors in patients with chronic orofacial pain. Secondly, differences in the psychosocial functioning of patients with various chronic orofacial pain conditions were explored. Lastly, a study was conducted to assess the impact of collaborative working with a neurologist specialising in headaches on diagnoses.

Methods: For the systematic review, a systematic online search was performed from 2006-2016. Forty-three studies were selected exploring anxiety and or depression. For the second and third projects, data were collected both retrospectively and prospectively from adult patients attending Orofacial Pain Clinic, at Kings College London Hospital, from January 2013 to January 2017.

Results: The systematic review showed severe to moderate depression (25.7%-46.7%) / anxiety (51.2%-54.3%) was associated with chronic orofacial pain levels and severity. Prospective data demonstrated possible anxiety disorder in 34% of neuropathic cases, 31.7% in the TMD group and 53.3% in the neurovascular group. Possible depressive symptoms in the neuropathic pain group were identified in 36.80% of cases, for TMD, in 23.10% of cases and for neurovascular in 42.60%. In the last project, an increased rate of diagnoses related to neurovascular (27.5% vs 19.0%) pain was observed in the 2016-2017 cohort. Decreased rates of neuropathic (55.6% vs 70.2%) and atypical/idiopathic pain (1.3% vs 5.4%) diagnoses were observed.

Discussion: Chronic orofacial pain significantly impacts the psychological well-being of individuals. Multidisciplinary input from psychology and neurology in chronic orofacial pain management is beneficial. Those with a neurovascular cause were highlighted as a subgroup that may require particularly intense psychological input.

Declaration

I Aalia Karamat declare that this thesis and the work presented has been composed and generated solely by myself as a result of my research. The title of the thesis is "Multidisciplinary management and psychological functioning in orofacial pain", and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where states otherwise by reference or acknowledgement, the work presented is entirely my own.

I confirm that

1. This presented work was done for the research degree of MPhil, King's College London, University of London
2. Been composed entirely by myself
3. Been solely the result of my own work
4. Not been submitted for any other degree or professional qualification.
5. Where I have consulted the published work of others, this is always clearly attributed

Signed: 

Date: 18th December 2018

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Abbreviations

AAOP	American Academy of Orofacial pain
ANOVA	Analysis of Variance
ATFP	Atypical Facial Pain
BMS	Burning Mouth Syndrome
CH	Cluster Headache
COFP	Chronic orofacial pain
CPAQ	Chronic Pain Acceptance Questionnaire
CI	Confidence Interval
DSM 4	Diagnostic Statistical Manual 4
EQ-5D	Euroqol-5 Dimensions
GAD-7	Generalised Anxiety Disorder-7
HC	Hemicrania continua
HR	Hazard Ratio
ICHD	International Classification for Headache Disorders
ICD-10	International Classification of Diseases version 10
IHS	International Headache Society
IASP	International Association for study of pain
MSPSS	Multidimensional Scale of Perceived Social Support
Ne	Neuropathic
Nv	Neurovascular
OFP	Orofacial pain
OHIP-14	Oral Health Impact Profile-14
OR	Odds Ratio
PCL	Patient Check List
PCS	Pain catastrophizing Scale
PD-Q	PainDETECT Questionnaire
PDAP	Persistent Dento-Alveolar Pain
PHQ-9	Patient Health questionnaire-9
PIFP	Persistent Idiopathic Facial Pain
PPTTN	Painful Post-Traumatic Trigeminal Neuropathy
PSEQ	Pain Self Efficacy questionnaire
PTSD	Post-Traumatic Stress Disorder
RDC/TMD	Research Diagnostic Criteria/Temporomandibular Disorders
SD	Standard deviation
SF-MPQ-2	Short Form McGill Pain Questionnaire
SUNA	Short-lasting Unilateral Neuralgiform Headache with cranial Autonomic symptoms
SUNCT	Short-lasting Unilateral Neuralgiform headache with Conjunctival injection and Tearing
TAC	Trigeminal Autonomic Cephalalgia
TMD	Temporomandibular disorders
TN	Trigeminal Neuralgia
VAS	Visual Analogue Scale

Chapter one

Literature Review

Literature Review

1.1. Introduction

Orofacial pain (OFP) is a complex, heterogeneous set of illnesses that present as pain in the region of the face and oral cavity. Chronic pain is a frequent cause of suffering and disability and a prevailing health and socioeconomic issue (Breivik et al., 2013).

1.2. Pain

The International Association for the Study of Pain (IASP) defines pain as "*an unpleasant sensory and emotional experience associated with actual and potential tissue damage"* (Derbyshire, 1999). Research has illustrated that there is a significant degree of subjectivity to the nature of pain experience, which includes both the central and the peripheral nervous systems, influenced by multiple pain-modulating factors such as past painful experience, cognitive components and the emotional state of an individual (Alencar, 2013). There is also enormous variability among individual's pain experiences (Renton et al., 2012b). Pain is activated through special receptors called nociceptors, which recognize actual or potential tissue damage (Hall and Guyton, 2011).

Pain that lasts and or recurs for more than three months or beyond the time of recovery is chronic pain (Merskey and Bogduk, 1994a). In chronic pain conditions, physiochemical changes occur within the neural pathways, making them hypersensitive to pain stimuli and the signals are repeatedly triggered. (Brookoff, 2000). Persistent pain impacts all domains of life, such as disturbed sleep, lack of concentration, mood disorders and feeling fatigued, frustrated, and anxious. The stress and depression generate family and employment issues resulting in a substantial burden on the healthcare system (Turk and Okifuji, 2002).

The prevalence of chronic pain, in general, is 43% in the UK; this equates to approximately just under 28 million of the UK population (Fayaz et al., 2016). According to a Canadian 2007/2008 pain survey, there is a reduced quality of life in more than 50% of individuals with pain, a negative impact on relationships of almost 29% and job loss or taking up less responsibilities for more than 50% of chronic pain patients (Sessle, 2011). Chronic pain conditions, in general, produce a significant degree of disability (Breivik et al., 2013) in the sufferer and are responsible for 21% of visits to the accident and emergency department and 25% of absenteeism from work annually (Jamison and Edwards, 2012).

1.3. Orofacial Pain

Orofacial pain is a noxious, painful experience in the region of the face and /or oral cavity (soft and mineralised tissues) (Carrara et al., 2010, IASP, 2016).

The prevalence of chronic OFP is 7% in the UK general population (Aggarwal et al., 2006) and 22% in the US, among individuals over the age of 18 years (Lipton et al., 1993), this disparity may be either due to variability in defining orofacial pain conditions or the methodology used in epidemiological research studies (Sharav and Benoliel, 2008). According to epidemiological studies, 21% - 30% of the population go through an orofacial pain experience at any time in their lives (Macfarlane et al., 2002a, Macfarlane et al., 2004). Gender distribution shows a higher prevalence in females compared to males (Macfarlane et al., 2002a). Women report more frequent and more severe orofacial pain, and the male to female ratio being 1:2 (Shinal and Fillingim, 2007).

Due to OFP, there is an increased loss of work days and healthcare system use (Shueb et al., 2015a). Healthcare resource use among chronic orofacial pain (COFP) patients is far greater compared to other dental patients due to multiple consultations with different specialities (Aggarwal et al., 2008b). There is also evidence of inadequate management and

multiple referrals (Beecroft et al., 2013). The average increase of £366 per person annually in consultation cost for COFP was calculated by Durham and colleagues (Durham et al., 2016). Breckons and colleagues investigated hidden out of the pocket and indirect costs of COFP with increased graded chronic pain scores (GCPS). They observed that, especially individuals with high GCPS, the out of pocket mean cost (treatment and assessment + time and travel + additional cost) was £551, and mean indirect costs (absenteeism) per person per six months were £2,992 compared to those with a low GCPS. Overall mean out-of-pocket costs were £333, and mean indirect costs were £1,242 per person per six months (Breckons et al., 2018).

According to an estimate, in the UK, an average of 42% of individuals with chronic pain were unable to work, and if they worked with pain, their productivity level reduced to one-third of normal (Bevan, 2016). Reduced level of productivity or absenteeism at work due to persistent OFP, costs employers almost £2,500 annually (Breckons et al., 2018). COFP continues after the expected time of recovery (Mehalick et al., 2013) and interferes with the basic functioning of the mouth and the face, reduces the work capacity of an individual and impacts interpersonal relationships with family members (Sharav et al., 2015). Seventy-three percent of individuals face problems with concentration because of persistent OFP and 59% with decision making (Breckons et al., 2018). Non-cancerous chronic pain is a substantial problem internationally (Jamison and Edwards, 2012).

Cultural differences were also identified in pain perception and sensitivity (Al-Harthy et al., 2016). Age, psychological state of mind (Carlson, 2007) and the presence of chronic painful conditions are linked to pain experience (Macfarlane et al., 2004). Pain in the orofacial region has a variable aetiology (Hargreaves, 2011). It includes disorders affecting or arising from the teeth, gums, salivary glands, temporomandibular joint, orofacial muscles; or the meninges, cornea, nasal structures and sinuses, these may all cause pain conditions complicating diagnosis (Hargreaves, 2011). The large representation of the trigeminal nerve in

the sensory cortex reflects the importance of orofacial pain and its significant physical, psychological and social impact (Renton et al., 2012b)

The anatomy of the orofacial region is complex and includes the teeth, nose, eyes, sinuses, temporomandibular joints, ears and musculoskeletal systems, which are all in close proximity to each other (Benoliel et al., 2008). Overall, approximately half of the sensory cortex is actively engaged in the perception and interpretation of signals from the orofacial region (Renton and Egbuniwe, 2015). The trigeminal nerve carries both intra-oral / extra-oral pain senses to the central nervous system via the trigeminal ganglion and sensory spinal nucleus in the brain stem. The intricate nature of the region and rich innervation challenges the clinician to attempt to comprehensively recognise the pathophysiology of pain of this area (Conti et al., 2003).

1.4. Pathophysiology of pain

The primary role of pain is the protection of an individual from tissue damage (Hall and Guyton, 2011). This applies to inflammatory and nociceptive pain only. Chronic pain is considered as a disease; this is manifested through loss of grey matter, neurophysiological and genetic changes within the brain. It is defined as pain persisting beyond the process of healing after the inflammatory response has halted (Woolf and Mannion, 1999, Woolf, 2010). Neuroimaging techniques illustrated that chronic neuropathic pain, such as trigeminal neuralgia leads to the reorganisation of grey matter at various cortical levels that are associated with sensorimotor and cognitive-emotional changes (DaSilva et al., 2008). The most frequently associated areas of TMD pain, according to a recent study, are the thalamus, the primary somatosensory cortex, the insula, and the anterior and mid-cingulate cortices (Suenaga et al., 2016).

From a neurobiological perspective, pain is of four types; nociceptive pain (which is about the perception of noxious stimuli), inflammatory pain (which is an adaptive/protective pain) and pathological, including neuropathic (caused by lesion or disease of neurosensory system) and dysfunctional (central pain of unknown cause) (Woolf, 2010).

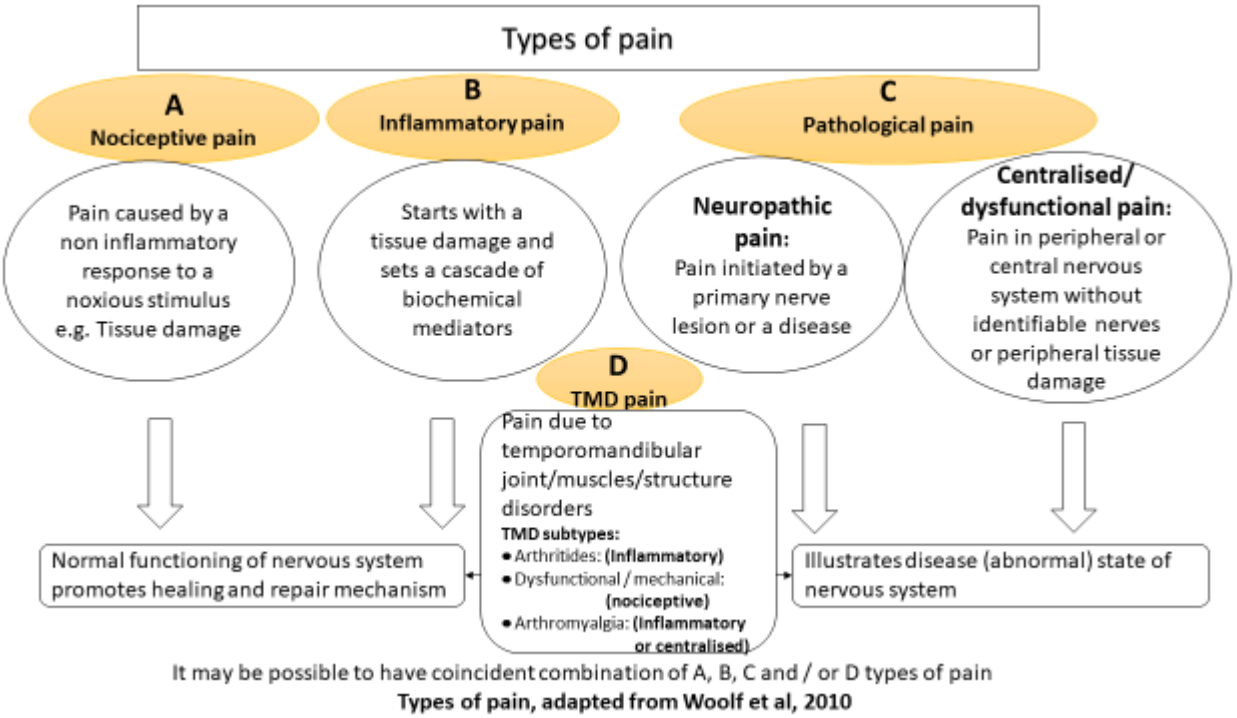


Figure 1.1 Types of pain

The character of the pain can vary, ranging from fast pain, lasting for 0.1 of a second after initiation by a stimulus and is expressed in various ways, for example, electric shock-like pain, sharp, pricking or acute pain to slow pain starting with a delay of 1 second, this intensifies over the subsequent seconds or minutes. It is also described in terms as burning, aching, nauseous or chronic pain and usually is indicative of tissue damage (Hall and Guyton, 2011). This may be related to the pain fibres transmitting the nociceptive signals or peripheral or central neuromodulators and transmitters.

Peripheral tissues contain free nerve endings in the form of pain receptors called nociceptors that are activated by mechanical, thermal or chemical stimuli (Hall and Guyton,

2011). Chemicals that propagate pain are bradykinin, histamine, proteolytic enzymes, acetylcholine, serotonin and potassium ions. In contrast, prostaglandins and substance P contribute to pain sensation through the enhancement of the sensitivity of nerve endings (Hall and Guyton, 2011).

The trigeminal nucleus in the pontine brain stem is connected to orofacial pain (Merrill, 2007). The trigeminal nerve transmits pain impulses from the periphery, that is, intraoral structures and the head (anterior part) to the brain (Merrill, 2007).

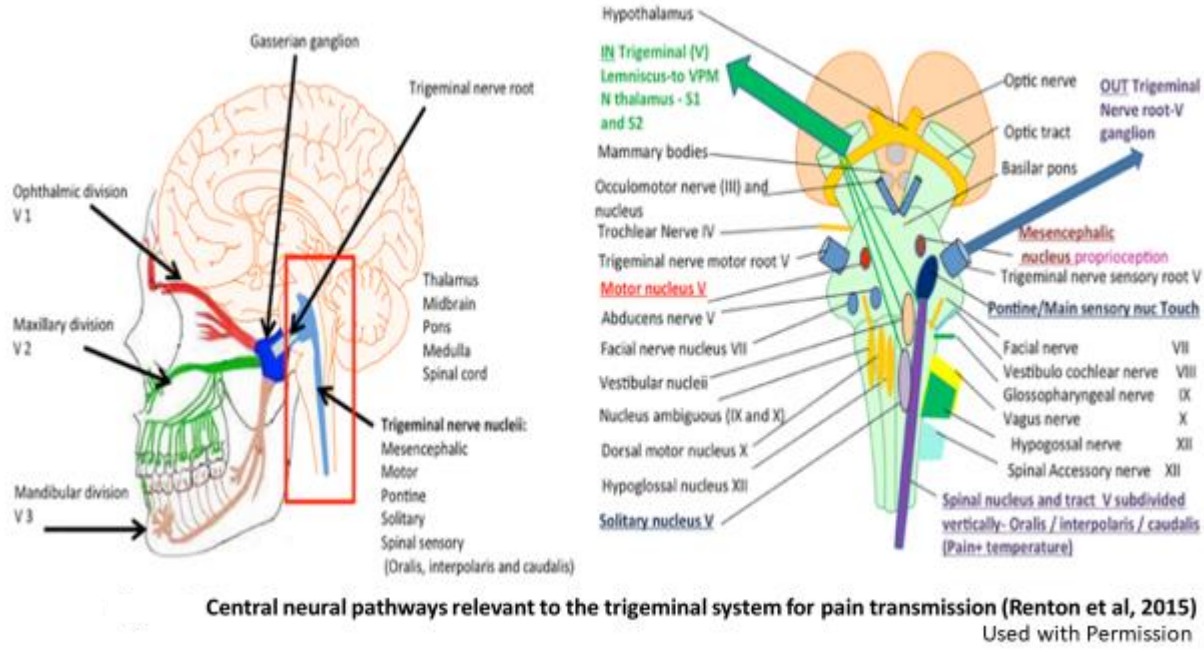
The sensory fibres are subdivided into mechanoreceptors called A-β mechanoreceptors and nociceptors called A-δ fibres, C fibres nociceptors and unmyelinated / thinly myelinated silent nociceptor fibres (Merrill, 2007).

The sensory fibres of the trigeminal nerve carry nociceptive stimuli from the periphery to the nucleus caudalis within the brain stem through the dorsal horn of the spinal cord via second order neurons. Signal modulation takes place at the brain stem in the form of inhibition or facilitation. The second order neurons ascend further across the midline to the thalamus where undifferentiated pain perception takes place. Third order neurons from the thalamus finally convey the stimuli to the brain cortex (somatosensory area), and the final discrimination and intensity of pain is determined (Christoforou et al., 2015).

Pain modulation, which is the inherent ability to alter pain intensity, occurs mainly in the midbrain, a periaqueductal region. This process also takes place in the spinal trigeminal nucleus (Conti et al., 2003). The final stage of pain perception, takes place in posterior parietal cortex of the brain (Conti et al., 2003).

At the level of sub-nucleus caudalis convergence (access of multiple afferent inputs on to a neuron) of nociceptive neurons from oral cavity, tooth pulp, temporomandibular joints,

muscles of mastication and facial skin takes place. This may be one of the reasons for the extensive referred pain experience in the orofacial region (Kojima, 1990). Anatomical organisation of sub-nucleus caudalis is adjacent to cervical spinal cord and is comparable to spinal dorsal horn (Gobel, 1981).



Central neural pathways relevant to the trigeminal system for pain transmission (Renton et al, 2015)
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Figure 1.2 Trigeminal system pain pathway

1.5. Orofacial pain association with other medical conditions

Studies have suggested that persistent orofacial pain may be associated with other comorbid medical conditions such as fibromyalgia, gastrointestinal problems, headaches, depression, stress and sleep problems, indicating this as part of general health issue (Stohler, 2001, Korszun, 2002).

Chronic pain is also related to physical disability, emotional disturbance and social problems (Sardá Júnior et al., 2012). Individuals in constant pain worry about other's opinion

and their views on the legitimacy of pain and may withdraw themselves from their social life (Turner-Cobb et al., 2015). The subjective pain experience is mediated by emotional, cognitive and social factors (Keefe et al., 2004). Its coexistence with depression reflects shared neurobiology, and its early recognition can help to prevent increased healthcare costs and improve patient management outcomes (Cocksedge et al., 2016). Genetic predisposition of COFP is also under investigation by researchers and may find a breakthrough to develop treatment strategies (Seltzer and Dorfman, 2004).

1.6. Psychological factors in acute to chronic pain transition

The brain limbic system processes emotions and modulates pain experience (Hansen and Streltzer, 2005). Anterior cingulate gyrus and right ventral prefrontal cortex are involved in the pain emotional response (Vastag, 2003). Psychosocial stress also produces activation of these centres. Sensory stimuli modulation involves serotonin and norepinephrine circuits and this may be the way experience of pain is perceived. This pathway is also involved in the aetiology of depression and its management with anti-depressants (Vastag, 2003).

Every individual is unique and responds differently to various painful stimuli (Eccleston, 2001). Research on pain psychology demonstrates that factors such as personality, gender, culture and age contribute towards response to painful stimuli; specific psychological traits have also been identified (Eccleston, 2001). Individuals, who are preoccupied and are hypervigilant of their bodily sensations, amplify their feelings of pain (Ferrari, 2002). Anxiety is a worry about an event, and fear is a reaction to those events; this accompanies a sense of loss of control, which further contributes negatively to the pain experience (Hansen and Streltzer, 2005). Patients' expectations (Turner et al., 1994), their culture (Ferrari, 2002), their belief about pain (Jensen et al., 1994), tendency to catastrophize, coping skills (Turner et al.,

2000), their self-efficacy (Martinez-Calderon et al., 2017) and illness behaviour determines the amount of pain an individual experiences.

Gatchel and colleagues proposed a model of three stages as a possible explanation for the conversion of acute pain into chronic one. Stage one is the acute pain phase, when an individual becomes hypervigilant and emotional. There may be an element of fear, and an individual may seek medical care. The second stage is a chronic phase when pain persists beyond the expected time of recovery. Psychological issues and behaviour changes develop. The third stage represents when due to chronic pain psychopathologies and exaggerated somatic symptoms develop (Gatchel et al., 2008).

1.7. Significance of psychological assessment of OFP patients

Psychological testing, according to the British Psychological Society (BPS) is the objective measure of psychological characteristics, and it helps to assess the abilities and qualities of an individual. This includes values, beliefs, motivation and/or personality (BPS, 2018). For psychological assessment of patients with pain, it is important to consider in addition to patients' emotional responses and beliefs, other important contributing social factors. Such as family interactions, life experiences and coping abilities of an individual (Jamison and Edwards, 2012).

Generalised anxiety disorder is an emotional state characterised by symptoms of feeling nervous and stressed with distressing thoughts and physical changes such as high blood pressure, increased heart rate, sweating, trembling and dizziness (ICD-10, 2016). Post-traumatic stress is an anxiety problem that comes after an intense traumatic episode and the memories are so severe that it disrupts lives (ICD-10, 2016). Depression is an emotional state in which an individual may lose interest and pleasure in daily activities; this is associated with

decreased energy levels, reduced concentration, weight gain or weight loss, feelings of worthlessness, guilt and there may be recurring suicidal thoughts (ICD-10, 2016).

Psychological problems such as anxiety/depression and personality disorders commonly exist in chronic pain individuals (Williams, 2013). Reported comorbid depression in pain clinics for chronic pain individuals was 52%, and in primary care settings, it was 27% (Bair et al., 2003). Anxiety disorder is another condition occurring commonly in chronic pain individuals; its prevalence is 23% (Narrow et al., 2002). Studies have demonstrated that individuals in pain are at risk of developing their first episode of anxiety and depression (Gerrits et al., 2014).

A cross-sectional study on COFP, specifically painful post-traumatic nerve injury, observed clinically significant anxiety in 51.2% of individuals and depression in 30% (Smith et al., 2013). Moderate to severe depression was observed in 48% of TMD patients (Guarda-Nardini et al., 2012). Chronic orofacial pain, such as TMD pain, interferes with day to day activity; individuals can feel embarrassed when eating socially and may have to make changes to their diet (Durham et al., 2011, Eaves et al., 2015). There is evidence of patients reporting cancer phobias in TMD pain and BMS (Stavrianos et al., 2009, de Souza et al., 2012).

Slade and colleagues conducted a prospective cohort study and observed that depression, perceived stress and mood are associated to pain sensitivity with a 2 – 3 times increase in the risk of having TMD (Slade et al., 2007). There are also reports of mood changes, a decreased willingness to be intimate (Durham et al., 2011) and under performance in employment among individuals with COFP (Garro et al., 1994, Durham et al., 2011).

1.8. Chronic Pain and attitudes/belief

Pain related physical and psychological impairment is observed to be associated with an individual's beliefs and perceptions (Turner et al., 2000). Pain beliefs are mental appraisals of a situation (DeGood and Tait, 2001), and are associated with psychological functioning (Turner et al., 2000) of an individual. Patients' beliefs can strongly predict utilisation of health care system (Brown et al., 2010). Pain perception and adherence to treatment is also influenced by belief (Jensen et al., 2007). Turner and colleagues suggested that patient's certain beliefs can determine physical disability perception and depression in chronic pain. (Turner et al., 2000).

Pain catastrophizing is linked to patients' beliefs and is characterised by magnifying pain threats and the feeling of helplessness (Quartana et al., 2009). Catastrophizing influences pain perception negatively and is considered to be important for the pain transition from acute to chronic (Burton et al., 1995).

A stressful encounter is evaluated by an individual through a cognitive appraisal process. Coping is when an individual attempts to manage internal or external demands that are appraised to exceed their psychological resource (Folkman et al., 1986). There are two types of coping, one is emotion focused, and the other is problem focused, by which an individual handles perceived stress (Folkman et al., 1986).

Galli and colleagues in 2010 investigated the predictive value of illness beliefs in orofacial pain patients. Their results indicated that pain belief can have serious consequences on an individual's life and was considered as a strong predictor of the treatment outcome of COFP (Galli et al., 2010). To reduce psychological distress and disability related to pain it was suggested to address catastrophizing (Turner et al., 2002). Another study indicated that an

illness belief can be modified and custom made interventions can alter the critical belief and result in better outcomes of treatment (Petrie et al., 2002).

1.9. Biopsychosocial model

1.9.1. Environmental factors influencing chronic pain

Chronic pain has a significant impact on relations and social life (Closs et al., 2009). Recent evidence on chronic orofacial pain demonstrated that painful post-traumatic trigeminal neuropathic pain patients were more affected compared to other chronic orofacial pains, scoring higher on the number of days absent from work (Haviv et al., 2017). If the pain was continuous, in the form of severe burning sensation and of stabbing type, there was more psychological distress/disability, and an individual was liable to give up work or there was a loss of productivity and more health care system utilization (Haviv et al., 2017). A study on TMD myofascial pain observed higher scores on social isolation in individuals with pain compared to those who were pain free (Schmitter et al., 2010).

The biopsychosocial model perceives objective disease and subjective illness as a complex interplay of biological and psychosocial circumstantial elements (Flor and Turk, 2015). There is a change of emphasis from depending solely upon pathophysiology to the patient's cognitive and emotional state, which conditions the response and subsequently impacts the pain experience (Turk et al., 2016). This perspective advocates a wide range of assessments incorporating psychological and behavioural factors in addition to biomedical problems. The presence of pain symptoms in a particular part of the body does not occur in isolation, it happens within a person with a distinct adaptive resource and learning behaviours (Turk et al., 2016). An individual lives in a society, and their social and environmental interactions implicitly determine pain experience, reaction to this experience and their adaptive response (Turk et al., 2016).

The Biopsychosocial model integrates a person's mind and body as interconnected entities (Bevers K et al., 2016). George Engel proposed the biopsychosocial model and introduced it in the 1970's (Borrell-Carrio et al., 2004). He was of the opinion that for a comprehensive understanding of patient's suffering of a disease, the clinician should address not only the biological aspect of the condition but the psychological and social dimensions must also be considered (Engel, 1977). Engel conceptualized an illness model and suggested that pain initially originates from a physical problem causing distress, initiating the behaviour of illness and progressing towards taking the sickness role by an individual (Gatchel et al., 2007).

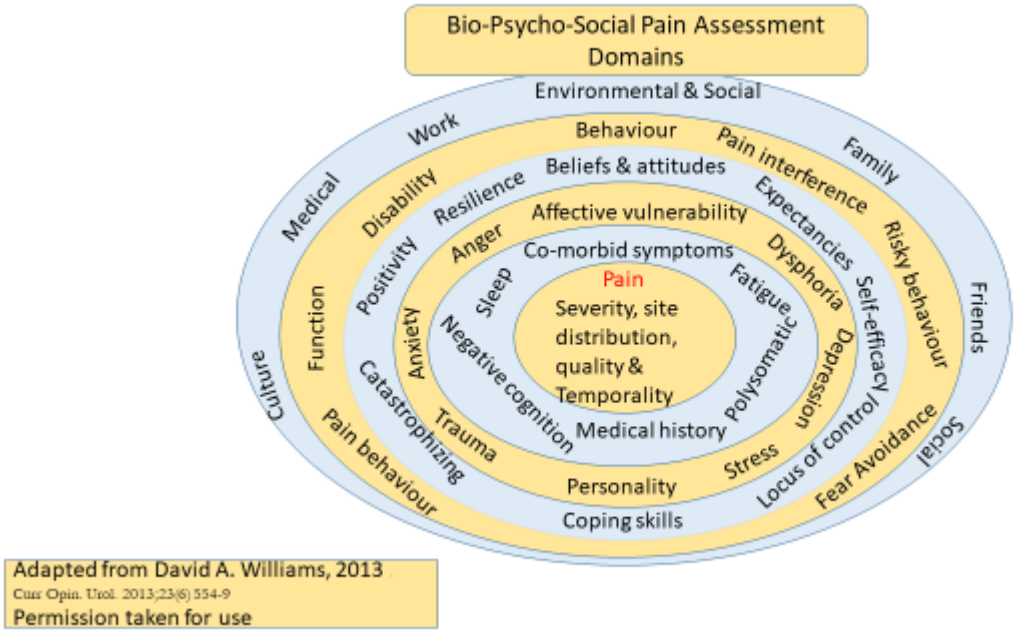

Figure 1.3 Biopsychosocial pain domains

1.9.2. Association between biopsychosocial model and patient centred assessment

Health service providers follow evidence based guidelines for clinical practice, which are important to improve quality and health outcomes (Grol, 2001). To deliver quality treatment,

the three key elements are patient safety, clinical effectiveness and patient experience (Britain and Darzi, 2008). To improve patient experience, patient centred care (PCC) recommends that reaching a diagnosis is only one aspect of the assessment process; it also requires consideration to the actual interpretation of patient's subjective understanding of illness / health, subsequently followed by giving patients the time and opportunity to think, reflect, understand their problem and make an informed decision (Borrell-Carrio et al., 2004). Promoting patient involvement is important in allowing their proactive role and responsibility of taking control of their own health and ensuring considerations to their needs and preferences are met (van Dulmen et al., 2015). The medical literature suggests it to be a cost-effective approach (Bertakis and Azari, 2011), it reduces patient's anxiety, improves satisfaction levels and feelings of wellness (Stewart et al., 2000, Oates et al., 2000).

1.10. Assessment and management of orofacial pain patient

The general assessment of the orofacial pain patient begins with taking a comprehensive history that includes; history of the presenting complaint, medical, dental and psycho-social history (Gilkey and Plaza-Villegas, 2017). In addition to this, conducting a physical examination, taking radiographs and laboratory tests to screen, evaluate, develop differential diagnoses and to establish a diagnosis are essential (Gilkey and Plaza-Villegas, 2017). The aim of the assessment is to gain a clear orofacial pain diagnosis and to recognise comorbidities that may impact on the progression of the pain condition and the patients' response to treatment. The purpose of OFP management is to control pain, to reduce functional disability and to improve general well-being and life quality (Zakrzewska, 2013a). Successful management of the patient with an OFP condition, is by providing the patient with a clear diagnosis and realistic management of the patients' expectations of outcomes (Cormier et al., 2016).

Different types of orofacial pain are managed according to their aetiologies. These are combinations of pharmacological and psychological therapies.

1.10.1. Antidepressants:

1. Tricyclic Antidepressants such as Amitriptyline and Nortriptyline are commonly used in orofacial pain (Lino et al., 2017). They are effective in TMD pain (Cascos-Romero et al., 2009) and also for neuropathic pain (Obata, 2017). Tricyclic antidepressants seem to inhibit reuptake of 5 hydroxy tryptamine (serotonin) and/or norepinephrine in the central nervous system (Rizzatti-Barbosa et al., 2003). Among these amitriptyline has more inhibitory action on serotonin uptake which may help to control persistent chronic pain. In addition to this it also blocks sodium channels which is likely to account for their analgesic effect in neuropathic pain management (Dick et al., 2007a)
2. Duloxetine / Venlafaxine (SNARI) are serotonin noradrenaline reuptake inhibitors. It has negligible effect on other receptors such as muscarinic, α-adrenergic and histamine H_1 receptors (Holliday and Benfield, 1995, Wong et al., 1995). These drugs cause a balanced inhibition of serotonin and noradrenaline (Baldessarini, 1990) and are used particularly for neuropathic pain (Ganzberg, 2010). Generally patients show better compliance with these medicines (Holliday and Benfield, 1995)
3. Fluoxetine (SSRI) is a selective serotonin (5hydroqtryptamine, 5-HT) reuptake inhibitor (Wong et al., 1995). It has an effective antidepressant activity, but no analgesic properties (Max et al., 1992). Its use in chronic orofacial pain can facilitate daily function and improve coping abilities (Ganzberg, 2010).

1.10.2. Antiepileptics:

1. Carbamazepine is an antiepileptic agent, usually used for neuropathic pain, especially trigeminal neuralgia (Vargas-Espinosa et al., 2012) and sometimes for headaches. This drug is considered to restrict neuronal excitation and enhance inhibition. The mechanism of action of antiepileptic medicines is not fully understood; however, the recognised basic mechanisms at cellular levels are, voltage gated ion channels (Na^{+}, Ca^{2+}, K^{+}) modulation, excitatory transmission reduction and amplification of inhibitory neurotransmission mediated by GABA (Deshmukh et al., 2011, Dick et al., 2007b, Ganzberg, 2010).
2. Pregabalin is an anticonvulsant medicine and is effectively used for neuropathic pain (Vargas-Espinosa et al., 2012). To produce its analgesic and anti-inflammatory action it acts as an antagonist of voltage gated Ca2+ channels and binds specifically to alpha-2-delta subunit (Ryder and Stannard, 2005, Verma et al., 2014).
3. Gabapentin is an oral antiepileptic medicine. Its receptor profile activity is not completely known. It was formed as a structural analogue of - aminobutyric acid (GABA) but did not act on any known receptors in the brain, including GABA receptors (Taylor, 1997). It is effective for selective neuropathic orofacial pain (Seto et al., 2011).
4. Lamotrigine belongs to an anticonvulsant group of drugs and is effective in trigeminal neuralgia, it blocks sodium channels of dorsal root ganglia and reduce ectopic discharge in the affected neurons and nerve endings (Jensen, 2002).

1.10.3. Psychological therapies (behavioural and cognitive therapy)

1. Cognitive Behavioural Therapy (CBT), according to British Psychological Society is a type of psychotherapy that helps individuals understand how they have

been trapped in their own thinking (cognition). It facilitates individuals finding a helpful way of thinking, reflecting, behaving and developing strategies and ways to come out of the trap of their own negative thinking loop. The techniques used are biofeedback, relaxation, exposure and cognitive restructuring and have been used in orofacial pain conditions (Matsuoka et al., 2017)

2. Cognitive analytic therapy (CAT) is a collaborative programme of therapy specifically tailored to an individual's need and their manageable achievable goals, in which therapist analyse the way individual think, feel and act. The development of an empathetic relation within boundaries helps patients to make sense of their situation and find ways of making changes for the better (Ryle and Kerr, 2003).
3. Acceptance and commitment therapy (ACT) and mindfulness based stress reduction (MBSR) for chronic pain management focuses on accepting pain rather than controlling it and thereby improving the emotional general wellbeing of an individual and engaging the patient in positive recreational activities such as sports (Sturgeon, 2014).

1.11. Classification of Orofacial Pain

Pain associations such as the International Association for Study of Pain (IASP), International Headache Society (IHS), American Academy of Orofacial Pain (AAOP) and Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) have published classifications for orofacial pain (Renton et al., 2012b).

The International Headache Society first published a classification for orofacial pain, neuralgia and headaches in 1988 (Okeson, 2008). This was redrafted in 2004, based on the aetiology and the structures involved. However, psychological factors were not considered. These are now recognised as important comorbid features in the presentation of orofacial pain

(Renton et al., 2012b, Smith et al., 2013). It was later considered to take into account both somatosensory and psychological elements during assessments (Okeson, 2008). This has led to dividing pain disorders into Axis I, considering the physical conditions (broadly divided into two categories, somatic and neurogenous), and Axis II, considering psychological conditions. All types of pain are influenced by psychological components, although persistent and chronic pains appear to have a wider component of psychological factors (ICHD, 2004, Okeson, 2008). The American Psychiatric Association (APA) included mental disorders such as anxiety disorders, somatoform disorders and mood disorders closely related to medical conditions including pain perception (Okeson, 2008).

To date, there is no single classification in use that is fully operationalised which can give an accurate diagnosis based on aetiology. The most systematic classification currently in use is by Woda and colleagues (Woda et al., 2005). According to this classification, chronic orofacial pain is divided into three broad categories, namely neurovascular, neuropathic and idiopathic (Egbuniwe and Renton, 2015)

Currently the International Classification of Headache Disorders has divided headaches and facial pain into primary headaches, secondary headaches, painful cranial neuropathies and other facial pains and headaches (ICHD-3, 2018).

The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) in 1992 published a classification system that assesses Axis I, the physical state and Axis II, psychological state of individuals with temporomandibular disorder pain (Schiffman et al., 2014).

Table 1.1. Classification/Diagnostic criteria of Orofacial pain conditions

Diagnosis and Pain types	Classification System / Description	Diagnostic Criteria
• **Temporomandibular Disorders**		
Nociceptive (disc entrapment), arthritides and muscular (inflammatory) **May be additional centralised or dysfunctional pain in long term conditions**	Diagnostic criteria / Temporomandibular disorders (Schiffman et al., 2014) (TMD pain; Non-neuropathic)	Time frame is pain of 30 days in the TMD area **A. Temporomandibular disorders** 1. Joint pain 2. Joint disorders 3. Joint diseases 4. Fractures 5. Congenital/developmental disorder **B. Masticatory muscles disorders** 1. Muscle pain 2. Contracture 3. Hypertrophy 4. Neoplasm 5. Movement disorders 6. Masticatory muscle pain attributed to systemic/central pain disorders **C. Headaches** 1. Headache attributed to TMD **D. Associated structures**
• **Neuropathic pain**		
Painful Post Traumatic Neuropathy (Benoliel et al., 2012).	ICHD-3-2016 Part 3 (13.1.2.3) **Description:** Unilateral facial or oral pain following trauma to the trigeminal nerve, with other symptoms and/or clinical signs of trigeminal nerve	**A.** A Spontaneous or touch-evoked (stimulus dependent) pain affecting one or more divisions of the trigeminal nerve that: Lasts from seconds to minutes / or is constant (>8h/day, >15 days/month) **B.** Develops within 3 months of an identifiable traumatic event to the painful area or relevant innervation. Continues for more than 3 months. Trauma, surgery, invasive dental treatment. Usually localised pain. Likely to cause dermatomal pain, may spread due to central mechanisms **C.** At least one clinically evident neurologic dysfunction: Positive sign 1. Hyperalgesia 2. Allodynia 3. Swelling or flushing and/or negative sign 4.Anaesthesia 5.Hypoesthesia **D.** Not better accounted for by another ICHD-3 diagnosis. Other causes are ruled out by history, physical examination, and special investigations if necessary **E.** Not attributed to another disorder **Diagnostic level** Fulfils criteria A,B and E Possible neuropathic pain (NP) Fulfils criteria A,B,C or D, and E Probable NP Fulfils criteria A,B,C,D and E Definite NP

Persistent dento-alveolar pain (PDAP) (Nixdorf and Moana-Filho, 2011)	International Association for the study of pain (IASP) Persistent (chronic) continuous pain symptom located in the dento-alveolar region and cannot be explained within the context of other diseases or disorders. May include Phantom tooth pain, painful neuropathy (non-traumatic), atypical odontalgia (Nixdorf and Moana-Filho, 2011)	**A.** Unilateral facial and/or oral pain fulfilling criterion C **B.** History of an identifiable traumatic event to the trigeminal nerve, with clinically evident positive (hyperalgesia, allodynia), and/or negative (hypo-aesthesia, hypo-aelgesia) signs of trigeminal nerve dysfunction **C.** Evidence of causation demonstrated by both of the following: 1. Pain is located in the distribution of the same trigeminal nerve 2. Pain has developed within 3-6 months of the traumatic event **D.** Not better accounted for by another ICHD-3 diagnosis
Burning mouth syndrome Secondary BMS; Burning mouth symptoms includes patients with systemic disease causing burning mouth symptoms	ICHD-3-2016 Part 3 Burning sensation in the mouth, occurring daily for more than two hours for three months, otherwise oral mucosa appears normal (ICHD-3, 2013)	**A.** Oral pain fulfilling criteria B and C **B.** Recurring daily for >2 hr per day for >3 months **C.** Pain has both of the following characteristics: 1. Burning quality 2. Felt superficially in the oral mucosa **D.** Oral mucosa is of normal appearance and clinical examination including sensory testing is normal **E.** Not better accounted for by another ICHD-3 diagnosis
Persistent idiopathic facial pain	ICHD-3-2016 Part 3 (13.11) Persistent facial and/or oral pain, with varying presentations but recurring daily for more than two hours per day over more than three months, in the absence of clinical neurological deficit (ICHD-3, 2013)	**A.** Facial and/or oral pain fulfilling criteria B and C **B.** Recurring daily for >2 hr per day for >3 months **C.** Pain has both of the following characteristics: 1. Poorly localized, and not following the distribution of a peripheral nerve 2. dull, aching or nagging quality **D.** Clinical neurological examination is normal **E.** A dental cause has been excluded by appropriate investigations **F.** Not better accounted for by another ICHD-3 diagnosis
Trigeminal Neuralgia	ICHD-3-2016 Part 3 (13.1)	**A.** At least three attacks of unilateral facial pain fulfilling criteria B and C

	A disorder of trigeminal nerve characterised by unilateral, brief, electric shock like pain episodes, with or without persistent background facial pain (ICHD-3, 2013)	**B.** Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution **C.** Pain has at least three of the following four characteristics: 1. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 min 2. Severe intensity 3. Electric shock-like, shooting, stabbing or sharp in quality 4. Precipitated by innocuous stimuli to the affected side of the face **D.** No clinically evident neurological deficit **E.** Not better accounted for by another ICHD-3 diagnosis
• **Neurovascular pain (Primary headaches)**		
Migraine	ICHD-3-2016 Part 1 (1) Recurrent throbbing headache, affecting typically one side of the head. This may or may not be accompanied with aura (ICHD-3, 2013)	**Diagnostic criteria** **A.** At least five attacks, fulfilling criteria B-D **B.** Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated) **C.** Headache has at least two of the following four characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) **D.** During headache at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phono phobia **E.** Not better accounted for by another ICHD-3 diagnosis
Tension type Headache 2.1-4	ICHD-3-2016 Part 1 (2) Frequent episodes of headache, typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting minutes to days. The pain does not worsen with routine physical activity and is not associated with nausea, but	**A.** At least 10 episodes of headache occurring on 1-14 days per month on average for >3 months (≥12 and <180 days per year) and fulfilling criteria B-D **B.** Lasting from 30 min to 7 days **C.** At least two of the following four characteristics: 1. Bilateral location 2. Pressing or tightening (non-pulsating) quality 3. Mild or moderate intensity 4. Not aggravated by routine physical activity such as walking or climbing stairs **D.** Both of the following: 1. No nausea or vomiting

	photophobia or phonophobia may be present (ICHD-3, 2013)	2. No more than one of photophobia or phono phobia **E.** Not better accounted for by another ICHD-3 diagnosis
Trigeminal Autonomic Cephalalgia	ICHD-3-2016 Part 1(3) Lateralised headache often with prominent cranial parasympathetic autonomic features which are ipsilateral to the headache (ICHD-3, 2013)	**A.** Headache attacks fulfilling all but one of criteria A-D for 3.1 Cluster headache, criteria A-E for 3.2 Paroxysmal hemicrania, criteria A-D for 3.3 Short-lasting unilateral neuralgiform headache attacks or criteria A-D for 3.4 Hemicrania continua **B.** Not fulfilling ICHD-3 criteria for any other headache disorder **C.** Not better accounted for by another ICHD-3 diagnosis
Other Headaches	ICHD-3-2016 Part 1 (4) Pain in the region of head (ICHD-3, 2013)	

1.12. Psychological assessment tools

Chronic orofacial pain considerably impacts on oral health related quality of life of individuals (Shueb et al., 2015a). There is a strong link between long standing orofacial pain and depression and anxiety symptoms. With impaired psychological function, there is a change in beliefs and cognitions. Slowly the capability of an individual with chronic pain to work reduces and they may retire early (Nilsson et al., 2013). It is important to measure the psychological function of such individuals to be able to have an understanding of their perspective and to provide tailored made treatment in line with stratified medicine.

These tools were selected by agreement between the orofacial pain team (neurology, psychology (local lead input), psychiatry, (Institute of psychiatry, psychology and neurosciences-IMPARTs team), oral medicine and oral surgery.

Table 2 shows the psychological questionnaires that were used for patients reporting orofacial pain.

Table 1.2. List of psychological questionnaires

Euroqol-5D	Measures quality of life with descriptive questions and visual analogue Scale.
GAD-7	Screens general anxiety levels
PHQ-9	Screen and diagnose depression.
MSPSS	Multidimensional state of perceived social support assesses support from family friends and other significant.
OHIP-14	Measures oral health related quality of life
PCL	Screen and diagnose post-traumatic stress
CPAQ	Chronic pain acceptance questionnaires assess how much the individual has accepted pain and how much it has influenced an individual
SF-MPQ-2	Short form McGill questionnaire provide descriptive information of pain experience
PD-Q	Pain detect is a screening tool to identify neuropathic component of pain
PCS	Pain catastrophizing scale measures various level of pain with psychosocial disability
PSEQ	Pain self-efficacy questionnaire measures self-efficacy beliefs of individuals

1.11.1. Euroqol-5Dimensions (EQ-5D-5L)

This is a generic instrument that measures health related quality of life through descriptive questions on mobility, self-care, usual activity, pain-discomfort and anxiety-depression. The responses are; no effect, slight, moderate, severe or extreme effect. For measuring health, a self-rated visual analogue scale is used from 0-100. Euroqol-5D has been shown to have construct validity and is reliable in measuring changes in the health perception of individuals (Hurst et al., 1997). Its convergent validity is established in persistent orofacial pain (Durham et al., 2015b).

1.11.2. General Anxiety Disorder-7 (GAD-7)

GAD-7 screens for general anxiety disorders using seven items related to individuals feeling anxious or irritable and not being able to relax or stop worrying over the past two weeks. The responses are numerical with each number given a rating level, 0=not at all, 1=several days,

2=more than half the days and 3=nearly every day. Studies have demonstrated it to be a reliable construct with 89% sensitivity and 82% specificity (Spitzer et al., 2006). In orofacial pain, for more comprehensive Axis II psychological evaluation of anxiety by researchers and specialist, GAD-7 is recommended (Schiffman et al., 2014).

1.11.3. Patient Health Questionnaire-9 (PHQ-9)

PHQ-9 is a health screening and depression diagnosing self-reporting tool. It has 88% sensitivity and 88% specificity. The nine item tool has good internal reliability with Cronbach's α to be0.89 (Kroenke et al., 2001). A cut-offs of 5, 10, 15, and 20 represents mild, moderate, moderately severe, and severe levels of depression (Kroenke et al., 2002). It is also recommended for patients having orofacial pain, to evaluate depression for the purpose of research or by specialists (Schiffman et al., 2014)

1.11.4. Multidimensional Scale of Perceived Social Support (MSPSS)

MSPSS is a self-reporting 12 item inventory assessing support from various social groups, including family and friends. It has adequate internal reliability with moderate construct validity (Zimet et al., 1988). Perceived social support for individuals with chronic pain is studied (Osborne et al., 2007), but specifically for COFP further research is needed.

1.11.5. Oral Health Impact Profile-14 (OHIP-14)

OHIP is an oral health impact profile measuring oral health related quality of life on three main domains, namely, functional limitation, physical pain and psychological impact. This contains fourteen questions following Locker's conceptual model of disease. Its reliability is high, with Cronbach's α of 0.88 (Slade, 1997). OHIP-14 is often used to measure oral health related quality of life for most of the orofacial pain conditions (Shueb et al., 2015b).

1.11.6. Post-traumatic stress disorder Check List (PCL) brief version

The brief version PCL screens individuals for post-traumatic stress disorder. In a study on orofacial pain patients, it has demonstrated sensitivity of 85% and specificity of 90% (Sherman et al., 2005).

1.11.7. Chronic Pain Acceptance Questionnaire-8 (CPAQ-8)

CPAQ-8 measures levels of acceptance of individuals with chronic pain. It has good internal consistency with an alpha score of ≥ 0.80 (Rovner et al., 2014). Studies have proved its reliability and validity in capturing pain willingness, that is accepting pain and engagement to activity (Fish et al., 2010). A systematic review on psychometric properties of CPAQ concluded that the questionnaire provides an adequate validity and reliability (Reneman et al., 2010). This questionnaire can also be used for psychological assessment of orofacial pain and headaches (Suen et al., 2018).

1.11.8. Short Form McGill Pain Questionnaire (SF-MPQ-2)

The short form McGill pain questionnaire assesses the character of pain by providing descriptive information. It is constituted of eleven sensory and four affective descriptors and has demonstrated sufficient sensitivity (Melzack, 1987). A modified version of this questionnaire (SF-MPQ-2) in which neuropathic symptoms were added and the rating scale was readjusted from zero to ten has indicated outstanding validity and reliability (Kachooei et al., 2015).

1.11.9. Pain Detect Questionnaire (PD-Q)

PD-Q is a screening tool for neuropathic pain, developed initially for low back pain, demonstrated a high sensitivity, specificity and positive predictive value accuracy of 84% in

palmtop computerised version and of 85%, 80% and 83% respectively in the paper version questionnaire (Freynhagen et al., 2006). It is an effective tool for orofacial neuropathic pain (Lopez-Jornet et al., 2017)

1.11.10. Pain Catastrophizing Scale (PCS)

PCS consists of thirteen questions. It measures three main components of catastrophizing, namely rumination, magnification and helplessness. Studies have proved it to be a reliable and valid measuring instrument (Sullivan et al., 1995). Cronbach's α value is 0.87 for total PCS (Osman et al., 2000).

1.11.11. Pain Self Efficacy Questionnaire (PSEQ)

PSEQ is pain self-efficacy questionnaire with high reliability and validity. The Cronbach α is 0.93 It is a thirteen item questionnaire that assesses how well an individual is coping with pain, with the belief that they can have control over their pain (Nicholas, 2007).

1.13. Project Rationale

Orofacial pain interferes with routine daily functions such as speaking, eating, chewing, and smiling (Sharav and Benoliel, 2008). When pain becomes chronic, the role of sensory input is reduced, and the cognitive affective pathway becomes prominent towards pain perception (Apkarian et al., 2005). A holistic management of COFP recommends a biopsychosocial approach that includes social, psychological and spiritual aspects (Siqueira and Morete, 2014). Psychosocial factors are inherent in chronic pain, and to achieve optimal treatment, its assessment needs to be considered (Williams, 2013).

Pain conditions are defined and classified according to their aetiology and distinct features (Daniel et al., 2008). It has been identified that psychosocial factors impact on pain perception in individuals complaining of persistent pain. It is also related to their physical and

psychological functioning (Daniel et al., 2008). Psychological treatments are becoming popular and effective chronic pain management strategies (Gustin et al., 2011). Understanding the psychological aspects of various chronic orofacial pain conditions may improve the assessment process and the development of comprehensive management strategies. In the past, a major focus was on investigating individual painful conditions and their psychosocial impacts. However, comparing different types of pains in the orofacial pain region was largely unexplored. This project explored psychological assessments of orofacial pain. Initially using, the paper version of multiple psychological questionnaires and later, this was substituted by an electronic tablet version through IMPARTS (Integrating Mental and Physical healthcare: Research, Training and Services). Evidence suggests that the integration of various questionnaires can provide an opportunity for an improved set of questions, reduce repetition and save time (John et al., 2016).

The National Pain Audit report 2010-2012, showed that for the management of chronic pain, specialised services are not equally available in all parts of the country, and it is important that NHS providers should attempt to establish multidisciplinary services countrywide considering the extent of disability it causes (Price et al., 2012). For OFP, there is no standardized care pathway and insufficient research on outcome measures (Beecroft et al., 2013).

Modern pain education is late coming to dentistry (Sessle, 2009). Dentists remain unfamiliar with chronic pain and, as a result, may often overlook the possibility of neuropathic pain rather than healthy toothaches (Zakrzewska, 2013). Toothache is the most common OFP and should be considered first, prior to considering other causes (Renton and Wilson, 2016). Tooth vitality tests are unpredictable, may give false positive results, indicating non-vitality in an unrestored, non-diseased vital tooth. This often leads to making diagnosis difficult and may result in unnecessary treatment decisions (Chen and Abbott, 2009). Orofacial pain patients can

feel confused and frustrated about their pain, and evidence shows that these patients may receive dental treatment for non-dental pain (Zakrzewska, 2009). There are many tissues like meninges, cornea, nasal and oral mucosa, tooth pulp, temporomandibular joint and related muscles from where pain may originate (Bereiter et al., 2008) in the orofacial pain regions making diagnosis challenging (Benoliel and Eliav, 2008). Therefore, COFP patients need a multidisciplinary management approach (Hals and Stubhaug, 2011).

This project aims

1. To explore the impact of psychological factors in patients with chronic orofacial pain (neuropathic and non-neuropathic).

2. To explore differences in psychosocial functioning of patients with various chronic orofacial pain conditions.

3. To assess the impact of collaborative working with a neurologist specialising in headache on diagnoses of patients attending an orofacial pain clinic (Karamat et al., 2018).

Chapter Two

Overview

Paper 1

Systematic review

2.1. Systematic Review: Anxiety and Depression in orofacial neuropathic and non-neuropathic pain: a systematic review

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Disclosure Statement

The authors report no conflicts of interest related to this study

2.1.1. Abstract

This systematic review explored the psychological function in patients with neuropathic and non-neuropathic orofacial pain conditions. A systematic online search of Medline (PubMed), and Ovid databases was performed from 2006-2016. Observational studies, including cross sectional, case control and case series and longitudinal prospective studies were included. Search strategy was restricted to studies in English with patients' aged 18 years and older. Forty-three articles were selected. Standardised PRISMA checklist was used to report studies for this review. Due to heterogeneity across studies, it was not possible to perform meta-analyses. Results showed that moderate to severe depression (25.7% - 46.7%) and anxiety (51.2% - 54.3%) were commonly observed in patients with chronic orofacial pain (COFP) and closely linked to pain severity. Comorbid conditions, such as chronic degenerative disorders, migraines or adverse life events increased the likelihood of psychological dysfunction in individuals. Females were more likely affected than males. Assessment of (Axis II) psychological impact of orofacial pain, predominantly focused on TMDs and rarely on other conditions including neuropathic pain / neurovascular pain. More research is needed to evaluate the psychological impact of multiple orofacial pain conditions in an individual, pre-condition psychological morbidity, the influence of social factors and delay in identifying psychological dysfunction.

Statement of Clinical Relevance

Chronic orofacial pain causes distress and disability. It affects life negatively and often leads to anxiety and/or depression and extensive use of the healthcare system. Holistic management for orofacial pain requires a biopsychosocial approach.

2.1.2. Introduction

Orofacial pain is a noxious, painful experience in the region of the face and /or oral cavity (IASP, 2018) . According to International Association for the Study of Pain (IASP), pain is defined as "*an unpleasant sensory and emotional experience associated with actual and potential tissue damage"*(IASP, 2018.) . Chronic pain continues after the expected time of recovery (Treede et al., 2015). There is evidence that pre-existing psychological factors can predict onset of chronic post-surgical pain (Macrae, 2008).

Patients with chronic pain frequently undergo a change in their beliefs and cognitions; as a result, these affective and cognitive pathways contribute to the sensory perception of pain (Williams, 2013). Over a period of time, individuals with chronic pain lose the capability to function optimally and some may retire early (Nilsson et al., 2013). Chronic pain conditions can cause a significant degree of disability (Breivik et al., 2013). It is responsible for 21% of visits to accident and emergency department and 25% of absenteeism from work annually, significantly increasing the economic burden (Jamison and Edwards, 2012). Orofacial pain (OFP) is specifically linked with increased work day loss and excessive use of the healthcare systems (Shueb et al., 2015a, Haviv et al., 2017).

OFP prevalence ranges from 17% - 26% with up to 11% considered chronic orofacial pain (COFP) (Macfarlane et al., 2002b). COFP is often associated with psychological disorders and there is a strong link between long standing orofacial pain and depression and anxiety symptoms, with impaired psychological function (Nilsson et al., 2013).

Without acknowledgement of psychological factors, pain management is limited and the recovery process often compromised, because differences in individual's psychological predisposition result in differential responses to pain (Ohrbach and Durham, 2017).

This review aims to evaluate the psychological function in patients with neuropathic and non-neuropathic orofacial pain.

2.1.3. Materials and Methods

The review protocol, including the search strategy was registered with Prospero, an international prospective register of systematic reviews 'PROSPERO' (Chien et al., 2012). (Registration number: CRD42016043703). The PRISMA checklist was used for reporting findings of the review. Due to heterogeneity of studies, meta-analyses was not possible. Cumulative evidence was assessed across the studies and were narrated (Moher et al., 2010).

2.1.3.1. Search strategy and selection criteria

The review included observational population based studies from 2006 to 2016. These were cross sectional, case series, and prospective and retrospective cohort studies. The information source was primarily from data bases, Medline (PubMed) and Ovid. Studies in English language which investigated at least one type of orofacial pain condition in adults (aged 18 and older) and explored psychological factors such as, depression, somatisation, post-traumatic stress disorder and catastrophizing were selected. Studies recruiting individuals under the age of 18 years and studies exploring dental and periodontal inflammatory conditions and their psychosocial impacts or influences were excluded.

Chronic primary pain is defined as a pain that exceeds three months duration (Treede et al., 2015); this was also applied to chronic pain in orofacial region. Psychology was defined as a scientific study of individual's behaviours and their mental processes (APA, 2017). According to World Health Organisation (WHO), depression is a mental disorder that presents with depressed mood, loss of interest or pleasure, decreased level of interest and concentration, disturbed sleep, lack of appetite with hopelessness and worthlessness (World Health, 1992). Depression can be associated with anxiety symptoms (World Health, 1992). Generalised

anxiety disorder was defined as six months of excessive worry on daily issues may be associated with autonomic symptoms (World Health, 1992). State anxiety is a temporary emotional arousal to a perceived threat and trait anxiety is a personality characteristic and pattern of response with anxiety to a threat (Gustin et al., 2011). Phobias, obsessive compulsive disorder and panic disorders were included in anxiety disorders. Phobia is a constant pronounced fear of a situation that can result in either avoidance or panic attacks (World Health, 1992).

2.1.3.2. Search terms

The key words used were psychosocial, psychological, depression, psychiatric comorbidity, post-traumatic stress disorder (PTSD) and anxiety disorder. These with "OR" and "AND" were used with the following conditions; orofacial pain, temporomandibular joint pain/disorder, trigeminal neuralgia, trigeminal nerve injury, burning mouth syndrome, persistent dento-alveolar pain, atypical facial pain and atypical odontalgia.

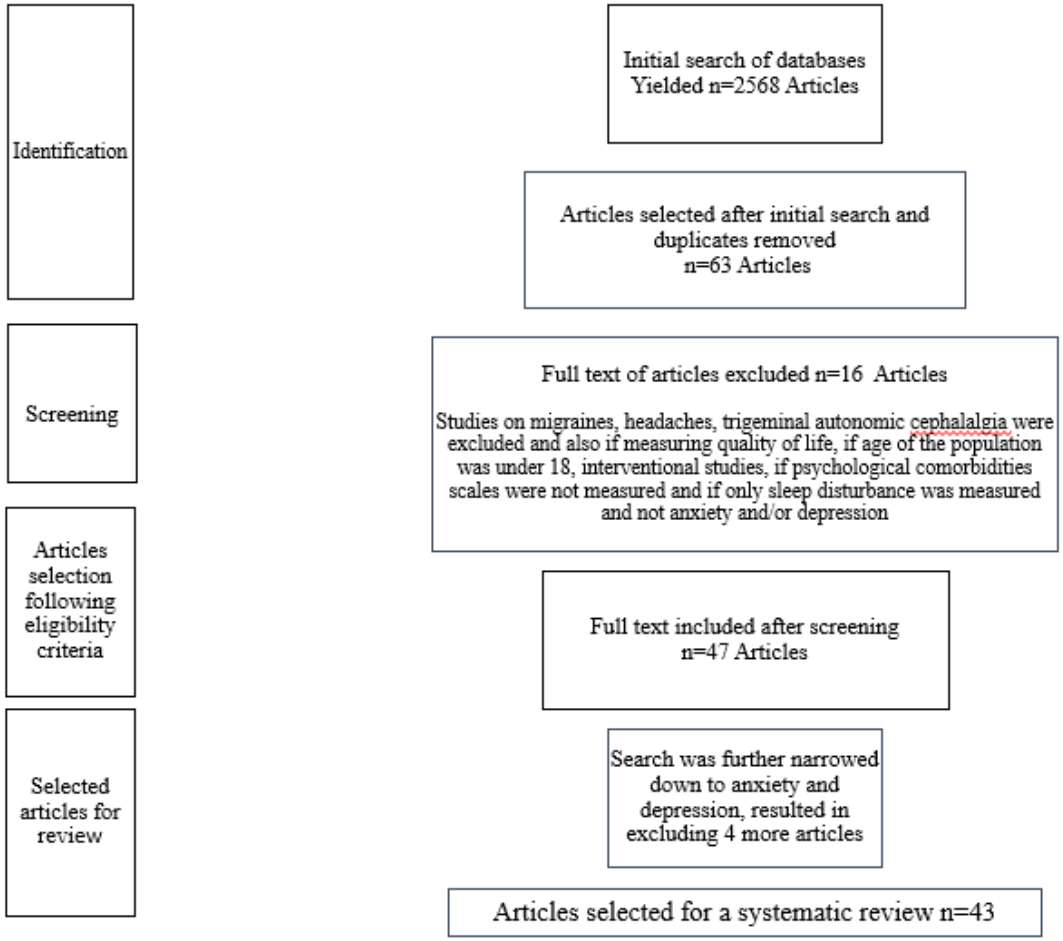
2.1.3.3. Outcome measures

The objective of this review was to investigate studies of psychological functioning (anxiety / depression) in patients with COFP and more specifically, to identify the prevalence of psychological dysfunction and its relationship with chronic pain and other functional constructs.

2.1.3.4. Data extraction

The initial search yielded 2568 articles. Suitable articles were identified for the review through the process of selection and filtration. On the basis of inclusion and exclusion criteria, 47 studies were selected. These were further reduced to 43, when inclusion criteria was narrowed to two conditions; anxiety and depression. This was done to reduce variability in the results,

since many of the psychological conditions could be broadly classified either under anxiety or depressive disorders.



PRISMA flow diagram for search strategy of systematic review

Figure 2.1.1 PRISMA flow diagram

Initially, the title and abstract of each article were read by one reviewer (AK) to establish their relevance for the review. After reading the abstract and ensuring that the article provided the necessary information for the review, the entire article was retrieved and read to further establish if it fulfilled the eligibility criteria. Any study that was unclear with regards to inclusion criteria was read by the second (JS), third (LM) and fourth (TR) reviewers. After discussion, consensus was reached for all articles included. Bibliographies of the selected articles were also manually searched.

The studies on COFP were categorised, according to the classification system of International Headache Society (ICHD-3, 2013, ICHD-3, 2018), Diagnostic Criteria Temporomandibular Disorders (Schiffman et al., 2014), International Association for the Study of Pain and American Academy of Orofacial Pain (Merskey and Bogduk, 1994a, IASP, 2011). All studies were assessed on the following parameters; type of study, type of pain under investigation, sample size, psychological scale used, psychological comorbidities under investigation, reported prevalence of psychological comorbidities in each study and the year of the study. The PRISMA check list was used to report studies for this review (Liberati et al., 2009). STROBE (Strengthening the Reporting of Observational studies in Epidemiology) (Von Elm et al., 2007) was used to assess quality of the studies (appendix 1.2).

Meta-analyses was not considered appropriate as there were insufficient number of studies with required level of homogeneity (Higgins and Deeks, 2008) in study design, COFP population under study and depression / anxiety scale used.

2.1.4. Results

The defining characteristics and key findings are summarised in Table 1.

2.1.4.1. Participant characteristics

The majority of included studies (25) focussed exclusively on the impact of TMD pain and its impact on psychological wellbeing (i.e. anxiety / depression). Seven studies recruited patients with a single neuropathic pain, 5 burning mouth syndrome (BMS), 2 post traumatic neuropathic pain (PPTN)). Eight studies compared patients with different OFP conditions, including studies comparing BMS with trigeminal neuralgia (TN), PPTN and TN with TMDs, idiopathic continuous orofacial neuropathic pain with TMDs, TN with TMDs, TMDs with migraine

(neurovascular pain), TN with atypical facial pain and BMS with atypical odontalgia (AO), including unspecified orofacial pain.

2.1.4.2. Gender

With the exception of the clinical trial study of PPTN patients where gender was evenly distributed (van Seventer et al., 2011), (mixed-gender) studies involving clinical OFP populations were predominantly female (range 61%-97%). One study included female (TMD) patients only (Xu et al., 2011). Aside from the community survey of elderly people (77% female) (Wan et al., 2012), studies recruiting participants from the community or (general) healthcare populations tended to have a small majority of females (range 51%-64%).

2.1.4.3. Study design

More than three quarters (33 or 76.6%) studies were cross sectional in design with OFP participants recruited from dental clinics in all but 3 of these studies; two studies measured (chronic) OFP and psychological symptoms in university student populations while another was a community-based survey of elderly people. Eight studies included a (healthy or non-OFP) control sample, recruited from the dental clinic, community or (general) healthcare service users. Four studies were retrospective examinations of patients with OFP, 3 were (general) population-based prospective cohort studies (with 5 year and 20-year follow-ups), one was a 4-month longitudinal study of a cohort of pre-university students, and one was a longitudinal study of cohorts recruited from the general population, primary care and secondary mental health care. An exception was made to also include one clinical trial of PPTTNI patients, as the study was a secondary analysis of trial data which specifically examined the association of post-intervention between the level of pain experienced and the degree of observed anxiety and depression. Almost half of studies were conducted (only) in Europe (21 or 48.8%), followed by Asia (8 or 18.6%), South America (5 or 11.6%) North America (4 or

9.3%), Middle East (2 or 4.7%) and Australia (1 or 2.3%); 2 studies were pan-continental (Europe-Middle East and Europe-North America). Sample size of studies varied widely; the median (range) clinical (OFP) and control (no OFP) sample sizes across cross-sectional/retrospective studies was 110.5 (22-1437) and 60 (31-200), respectively, while the median (range) overall sample size of prospective cohort /longitudinal studies was 614 (153-6040). Very few studies explicitly considered power of the study.

The main findings of selected studies are presented in the Table 1.

2.1.4.4. Studies characteristics

There were 20 studies (Smith et al., 2013, van Seventer et al., 2011, Buljan et al., 2008, de Souza et al., 2012, Lopez-Jornet et al., 2015, Sevrain et al., 2016, Reiter et al., 2015, Kim et al., 2010, de Lucena et al., 2012, Kotiranta et al., 2015, Fillingim et al., 2013, Bertoli et al., 2007, Guarda-Nardini et al., 2012, Xu et al., 2011, Nifosi et al., 2007, Kindler et al., 2012, Giannakopoulos et al., 2010, Gustin et al., 2011, Castro et al., 2008, Macianskyte et al., 2011) investigating the association of OFP with anxiety and depression, 7 studies (Bakhtiari et al., 2010, Schmitter et al., 2010, Pesqueira et al., 2010, GaldOn et al., 2006, Stavrianos et al., 2009, Davis et al., 2014, Wan et al., 2012) with anxiety only and 16 studies (Lee et al., 2008, Manfredini et al., 2010a, Dougall et al., 2012, Reissmann et al., 2008, Ozdemir-Karatas et al., 2013, Komiyama et al., 2014, Manfredini et al., 2010b, Rodrigues et al., 2012, Licini et al., 2009, Macfarlane et al., 2009, Cioffi et al., 2014, Komiyama et al., 2012, McMillan et al., 2010, Takenoshita et al., 2010, Gerrits et al., 2014) with depression only. Twenty-one studies (Smith et al., 2013, de Souza et al., 2012, Sevrain et al., 2016, Reiter et al., 2015, Lee et al., 2008, Manfredini et al., 2010b, de Lucena et al., 2012, Celic et al., 2011, Manfredini et al., 2010a, Rodrigues et al., 2012, Licini et al., 2009, Reissmann et al., 2008, Guarda-Nardini et al., 2012, Pesqueira et al., 2010, Xu et al., 2011, Macfarlane et al., 2009, Kindler et al., 2012, Wan et al.,

2012, McMillan et al., 2010, Macianskyte et al., 2011, Takenoshita et al., 2010) provided prevalence data for anxiety and/or depression.

2.1.4.5. Orofacial pain assessment criteria

Nearly 30% of the studies (12) did not specify whether the assessment criteria/classification for OFP followed the established diagnostic criteria for OFP conditions considered in their paper. Thirty-one studies followed an established diagnostic criterion for the OFP conditions considered. These included Research Diagnostic Criteria/ TMD (RDC/TMD), International Headache Society (IHS) criteria, American Academy of Orofacial Pain (AAOP) criteria and International Association for the Study of Pain (IASP) criteria. Furthermore, Liverpool criteria for trigeminal nerve pain was used by one study while another used Xu-chen Ma + Zen-Kang Zhang classification for TMD pain.

2.1.4.6. Psychological screening tools used

Twenty-one studies used a single psychological tool while 22 studies used a combination of psychological assessment tools. The Research Diagnostic Criteria/Temporomandibular Disorders (RDC/TMD) (Axis II) questionnaire, Symptom Check List -90-Revised (SCL-90-R) and Hospital Anxiety and Depression Scale (HADS) were most commonly used to screen for anxiety and/or depression.

Table 2.1.1. Studies Characteristics

Studies Characteristics						
Study	**Study Type**	**Pain Type**	**N & Gender distribution**	**Psychosocial scales**	**Psychological Comorbidity**	**Prevalence in percentages**
1. (Smith et al, 2013) (UK)	CSS	Ne (PPTNI)	89; M:31%, F: 68.5%	HADS	Anx Dep (Cl Sig)	51.2% 30.0%
2. (Reiter et al., 2015) (Israel)	ROS	TMD Acute n= 49,Ch n=139	207 M: 24%,F: 76%	RDC/TMD SCL-90-R	Anx (Mod/Sev) Dep (Mod/Sev)	54.1% (29.5/24.6) 56% (33.3/22.7)
3. (Lee et al., 2008) (China)	CSS	TMD	87; M:11.5%,F:88.5%	RDC/TMD	Dep (Mod/Sev)	42.5% (26.4/16.1)
4. (Manfredini 2010b) (Italy Israel Netherland)	CSS	TMD Acute n=293 Ch n= 856	1149 M: 20%, F: 80%	RDC /TMD (SCL-90)	Dep (Mod/Sev)	Acute 45.0% (23.1/21.9) Ch 47.7% (25.1/22.6)
5. (Schmitter et al., 2010) (Germany)	CCS	TMD	150; M: 31%, F: 69%	TICS	Stress levels Work discontent Social isolation	 - -
6. (Cioffi et al., 2014) (Italy)	CSS	TMD (MP) & Migraines A. MP, B. Migraine C. MP + Migraine	781; M:22%, F: 78% n = 676 n = 39 n = 66	RDC/TMD (SCL-90)	Dep	Mod -
7. (Dougall et al., 2012) (USA)	RS	TMD	207; M: 22%, F: 78%	RDC/TMD SCL-90, BDI-II	Dep	- -
8. (van Seventer et al., 2011) (UK, Netherland, Canada)	SA PCT	Ne (PPTNI)	254; M: 49%, F: 51%	HADS	Anx Dep	- -
9. (Kim et al., 2010) (Korea)	CCS	TMD Trauma n=34 TMD no trauma n=340	374; M: 29%, F: 71%	SCL-90-R	Anx Dep	- - -
10. (de Lucena et al., 2012a) (Brazil)	LPS	TMD Cases n=99 Controls no TMD n=54 Between two time periods	153; M: 46%, F: 54%	HADS	Anx Cases (TMD) Controls (no TMD) Dep Cases (TMD) Controls (no TMD)	T1 61.6% / T2 60.6% T1 22.2% / T2 37.0% T1 16.2% / T2 26.3% T1 5.6% / T2 14.8%
11. (Celic et al., 2011) (Croatia)	CSS	TMD Acute n=126, Ch n=28	154; M: 24%, F: 76%	RDC/TMD (SCL-90-R)	Dep (sev)	19.5%

12. (Ozdemir-Karatas et al., 2013) (Turkey)	CSS	TMD	104; M: 38%, F: 62%	RDC/TMD SCL-90-R, GCPS	Dep, Som Psychosocial disability	- 26.0%
13. (Kotiranta et al., 2015) (Finland)	CSS	TMD	399; M: 17%, F: 83%	RDC/TMD SCL-90-R GCPS, NRS, PCS	Dep	- - -
14. (Komiyama et al., 2014) (Japan)	CSS	TMD	1437; M: 29%, F:71%	RDC /TMD	Dep	-
15. (Fillingim et al., 2013) (USA)	Pr Co St	TMD T1 C n= 3263 T2 TMD n= 260, T2 C n= 2477	2737 (T2); M: 40%, F: 60%	STAI, SCL-90-R PSS, PCL, PCS	Anx, Dep	- -
16. (Komiyama et al., 2012) (Japan)	CSS	Ne: BMS, n= 282 TN, n= 83	365; M: 20%, F 80%	RDC/TMD	Dep	-
17. Wan KY et al,2012 (Hong Kong)	CS CBS	OFP CD: 200, IE: 200	400	MOPDS GHQ-12	Psychosocial Disability Psychological Distress	- CD: 4% IE: 11.0%
18. (Gustin et al., 2011) (Australia)	CCS	Ne & TMD TNP n = 24, TMD n= 21,C n=38	83; M: 24%, F: 76%	STAI, BDI PCS	Anx, Dep	- -
19. (Manfredini et al., 2010a) (Italy)	CSS	TMD	111; M: 19%, F: 81%	RDC / TMD, GCPS, SCL-90-R	Dep (Mod/Sev)	41.4% (1.8/39.6%)
20. (Rodrigues et al., 2012) (Brazil)	CSS	TMD OFP n= 54, C n= 129	183; M:41.5%,F:58.5%	RDC/TMD	Dep (Mod/Sev) Cases C	24.0% (20.0/4.0) 16.4% (15.5/0.8)
21. (Licini et al., 2009) (Italy)	CSS	TMD	308; M: 25% F: 75%	RDC/TMD	Dep (Mod/Sev)	65.7% (13.3/52.6)
22. (Reissmann et al., 2008) (Germany)	CSS	TMD	225; M: 14%, F: 86%	RDC/TMD	Dep (Mod/Sev)	47.6% (21.8/25.7)
23. (Bertoli et al., 2007) (USA)	RS	TMD	445; M: 9% F: 91%	PCL-C SCL-90-R	Dep	- - -
24. (Buljan et al., 2008) (Croatia)	CSS	Ne (BMS) Cases n=42, C No BMS n=78	120; M: 39% F: 61%	BAI SDS	Anx Dep	- -
25. (de Souza et al., 2012) (Brazil)	CS CCS	Ne (BMS) BMS; n=30 C; n=31	61; M: 3% F:97%	HRSD BDI STAI	Anx Dep Cancer phobia Social phobia Hypochondria	BMS 36.7%, C 9.7% BMS 46.7%, C 12.9% BMS 46.7%, C 6.5% BMS 30.0%, C 20.0% BMS 20.0%, C 3.2%
26. (Lopez-Jornet et al., 2015) (Spain)	CS CCS	Ne (BMS) Cases n=70 C n=70)	140; M; 9% F: 91%	HADS	Dep Anx	- -

27. (Guarda-Nardini et al., 2012) (Italy)	CSS	TMD	110; M: 19% F: 81%	HARS, HDRS SCL-90-R	Anx Dep Overall (Mod/Sev)	 48.0% (30-18%)
28. (Pesqueira et al., 2010) (Brazil)	CSS	TMD	150	STAI RDC/TMD	Anx; Trait anxiety State anxiety	66.7% 71.3%
29. (McMillan et al., 2010) (Hong Kong)	CS CCS	OFP n= 200; C n = 200	400; M: 36%, F: 64%	SCL-90	Dep	26.0%
30.(GaldOn et al., 2006) (Spain)	CSS	TMD MP n = 58 Articular n = 56	114; M:11%, F: 89%	BSI-18	Anx, General distress	- -
31. (Xu et al., 2011) (China)	CSS	TMD	162; F	SCL-90-R	Anx Dep	53.8% 76.9%
32. (Castro et al., 2008) (Brazil)	CSS	Ne (TN & TMD) TN n=15, TMD n=15	30; M: 27%, F: 73%	HADS	Anx Dep	- -
33. (Davis et al., 2014) (USA)	CSS	TMD	50; M: 8%, F: 92%	STAI PCS	Anx	-
34. (Macfarlane et al., 2009) (UK)	Pr Co S	TMD	337; M: 43%, F: 57%	CES-D PSS	Dep Stress	35.1% 53.7%
35. (Stavrianos et al., 2009) (UK)	CSS	TMD	22; M: 36%, F: 64%	IAS	Anx (Hypochondriac fears and beliefs)	-
36. (Nifosi et al., 2007) (Italy)	CSS	TMD Ch TMD + Comorb n=19 Ch TMD only n= 14	63; M: 25%, F: 75%	HARS, HDRS SCL-90-R	Anx (Diag) Dep (Diag) Anx and Dep (Sym)	15.9% 20.6% Anx Mod - Dep Mild
37. (Sevrain et al., 2016) (France)	RS	Ne (BMS)	35; M: 9%, F: 91%	HADS	Anx Dep Anx/Dep	54.3% 25.7% 34.3%
38. (Bakhtiari et al., 2010) (Iran)	CS CCS	Ne BMS n = 50 HC=50	100, M: 17%, F: 83%	Cattell anxiety scale	State anxiety Trait anxiety	- -
39. (Macianskyte et al., 2011) (Lithuanian)	CSS	Ne & IP TN n = 30, ATFP n = 30	60; M: 15%, F: 85%	CAS BDI	Anx Dep (Mod/Sev)	- TN 76.7% (30.0/46.7) ATFP 0%
40. (Kindler et al., 2012) (Germany)	LPS	TMD MP n = 50, JP n = 122	6,040; M: 49%, F: 51%	CID-S	Anx (Symptoms) Dep (Symptoms)	JP 64.8%, No JP 47.1% MP 78.0%, No MP 47.3% JP 49.2%, No JP 28.3% MP 46.0%, No MP 29.0%
41. (Takenoshita et al., 2010) (Japan)	CSS	Ne & IP BMS n=125, AO n = 37	162; M: 13%, F: 87%	SDS	Dep tendencies	32.1% BMS 33.3% AO

42. (Giannakopoulos et al., 2010) (Germany)	CSS	TMD MP n=88, JP n=43, Non TMD FP n=45, C n=46	222; M: 27%, F: 73%	HADS	Anx Dep	- -
43. (Gerrits et al., 2014) (Netherland)	LCS	OFP	614; M: 39% F: 61%	DSM-IV CIDI Version 2.1CIDI	Anx/Dep	B 3.9% F-up 15.5%

Note: Only percentages of psychological functioning impact of orofacial pain conditions were taken.

Abbreviations: Cross section study (CSS), Retrospective observational study (ROS), Case control study (CCS), Longitudinal population based study (LPS), Longitudinal cohort study (LCS), Prospective cohort study (Pr Co S), Retrospective study (RS), Community based survey (CBS), Secondary analysis of a placebo – controlled clinical trial (SA, PCT) Sample size (n), Males (M), Females (F), Healthy Control (HC), Community Dwellers (CD), Institutionalised Elderly (IE), Orofacial pain (OFP), Trigeminal Nerve Injuries (TNI), Painful Post Traumatic Nerve Injury (PPTNI), Trigeminal Neuralgia (TN), Burning Mouth Syndrome (BMS), Temporomandibular Disorder pain (TMD), TMD Muscle pain (MP), TMD Joint pain (JP), Neuropathic Pain (Ne), Idiopathic pain (IP), Atypical Odontalgia, (AO), Atypical Facial pain (ATFP), Hospital Anxiety and Depression Scale (HADS), Graded Chronic Pain Scale (GCPS), Numeric rating scale (NRS), Manchester orofacial pain disability scale (MOPDS), General health questionnaire (GHQ-12), Composit International Diagnostic Interview, version 2.1 (CIDI), Zung's Self-Rating Depression scale (SDS), Composite international diagnostic-screener (CID-S), Beck Depression Inventory (BDI), Covi's Anxiety scale (CAS), Cattell anxiety scale (CtAS), Trier Inventory for chronic stress (TICS), Research Diagnostic Criteria / Temporomandibular Disorders Axis II questionnaire (RDC/TMD), Symptom checklist-90-revised (SCL-90-R), Hamilton anxiety rating scale (HARS), Hamilton depression rating scale (HDRS), Illness attitude scale (IAS), Centre for epidemiological studies scale (CES-D), Perceived stress scale (PSS), State anxiety inventory (STAI), Pain catastrophizing scale (PCS), Brief symptom Inventory-18 (BSI-18), Beck's Anxiety Inventory (BAI), Anxiety (Anx), Depression (Dep), Somatisation (Som), State Anxiety (St Anx), Trait Anxiety (T Anx), Post-Traumatic Stress Disorder (PTSD), Catastrophizing (Cat), Clinical significant (Cl Sig), Moderate (Mod), Sever (Sev)

2.1.4.7. Anxiety, depression and phobias prevalence of orofacial pain

The prevalence of depression and/or anxiety disorder in COFP was reported in 21 studies. Clinically significant anxiety was found in 51.2% of individuals and depression was in 30.0% of cases of painful post traumatic neuropathic pain (Smith et al., 2013). Anxiety symptoms were identified in 54.3% of individuals suffering with BMS while depression was identified in 25.7% of individuals (Sevrain et al., 2016). Major depressive disorders in BMS were observed in 46.7% of individuals. Generalised anxiety disorder in BMS was identified in 36.7% of cases and cancer phobia in 46.7% of patients with BMS (de Souza et al., 2012). Severe depression was demonstrated in 18% of individuals with TMD while moderate depression was observed in 30% of cases (Guarda-Nardini et al., 2012).

Three studies (Gustin et al., 2011, Castro et al., 2008, Macianskyte et al., 2011) compared different types of OFP. Gustin and colleagues compared two types of pain, neuropathic (TNP) and nociceptive (TMD). Both TNP and TMD patients were significantly (but comparably) impaired in domains of anxiety (state or trait anxiety) and depression when compared with controls (Gustin et al., 2011). Psychological components were evaluated in patients with TN and TMD by Castro and colleagues; the authors reported that there was, on average, mild depression and moderate anxiety in both groups, although, no statistical differences were found between the patient groups (Castro et al., 2008). Macianskyte and colleagues investigated TN and atypical facial pain and observed that TN patients evidenced significantly higher levels of pain perception and depression (76%) (Macianskyte et al., 2011). Reissmann and colleagues, found moderate to severe depression in, 45% of patients with TMD muscle pain, 53% in TMD joint pain and 47% in TMD muscle and joint pain together (Reissmann et al., 2008).

2.1.4.8. Association between pain chronicity and pain severity with psychological symptoms

Patients with severe pain showed elevated levels of depression on HADS for painful post-traumatic neuropathic pain (Smith et al., 2013). Every two point decrease in levels of pain (0-10 numeric rating scale) was associated with 1.5 points improvement in anxiety (HADS) and 1.2 points improvement in depression (HADS) (van Seventer et al., 2011). A positive association of levels of depression (r=0.63) and anxiety (r=0.55) with BMS symptom severity was also observed (Buljan et al., 2008). Similar observations among elderly individuals were seen (Bakhtiari et al., 2010).

Reiter and colleagues compared chronic TMD with acute TMD pain. Depression was more prevalent in patients with chronic TMD pain, and severity of depression and anxiety increased with higher graded chronic pain scores (Reiter et al., 2015). An association between state-anxiety and chronic TMD pain was observed by Pesqueira and colleagues (Pesqueira et al., 2010). TMD pain with trauma history also illustrated elevated psychological dysfunction with pain severity (Kim et al., 2010). Celic and colleagues found multiple pain sites were associated with higher levels of depression (Celic et al., 2011). Guarda-Nardini and colleagues found that diffuse pain and high intensity pain in chronic TMD patients were associated with increased levels of anxiety and depression but pain duration and its location shared no relationship with psychological symptoms (Guarda-Nardini et al., 2012) .

Xu and colleague observed for grade III pain, anxiety was identified in 53.8% of individuals and depression was in 76.9% of individuals (Xu et al., 2011). Lee and colleagues identified moderate to severe depression in 42.5% of TMD cases and psychosocial dysfunction (on grade III/IV pain) in 15% of cases (Lee et al., 2008). Manfredini and colleagues carried out two studies on TMD pain patients. In the first study, severe depression was found in 39.6% of individuals and moderate depression in 1.8% of individuals. However, no statistically

significant correlation between graded chronic pain levels and depression levels were observed (Manfredini et al., 2010a). In the second study the authors identified high levels of pain related disability in patients with graded chronic pain scores (GCPS) of III / IV; there was severe depression in 21.4% of patients' and a strong association between pain related disability and depression (Manfredini et al., 2010b). Similar findings were observed by Ozdemir-Karatas et al (Ozdemir-Karatas et al., 2013) and Kotiranta et al (Kotiranta et al., 2015) study.

Rodrigues and colleagues conducted a study on university students with TMD pain; moderate depression was observed in 20% of students, severe depression in 4% of students while severe levels of pain were reliably associated with more severe depression (rho = 0.29) (Rodrigues et al., 2012).

Evidence of cancer phobia and heart disease phobia in individuals with TMD pain was found by Stavrianos and colleagues (Stavrianos et al., 2009). There was a linear relationship between symptoms level for the two phobias (r = 0.65). Regression analysis indicated that heart disease phobia acted as a predictor for cancer phobia (Stavrianos et al., 2009). Davis and colleagues observed increased pain perception levels in individuals with pain related worry in OFP (Davis et al., 2014). Psychological distress in elderly people with COFP was in 11% of institutionalised individuals compared to just 4% of community dwellers reported by Wan and colleagues (Wan et al., 2012).

2.1.4.9. Orofacial pain subtypes, multiple diagnosis and variability in psychological impact

Bertoli and colleagues reported that psychological dysfunction was significantly associated with TMD muscle pain in patients having post-traumatic stress disorder symptoms (Bertoli et al., 2007). Fillingim and colleagues found that anxiety and depression can be a predictor for TMD pain onset and chronicity (Fillingim et al., 2013). Kindler and colleagues

identified similar trends for anxiety and depression among patients with TMD pain subtype (Kindler et al., 2012), although notably depressive symptoms were strongly related to joint pain while anxiety symptoms were strongly related to muscle pain (Kindler et al., 2012). Nifosi et al and Schmitter et al found that muscle pain in TMD patients tended to present with more psychological problems and stress (Nifosi et al., 2007) (Schmitter et al., 2010). Anxiety in a TMD muscular group of patients was also significantly higher compared to an articular group in the GaldOn study (GaldOn et al., 2006). de Lucena and colleagues compared two separate time periods in the pre-university students, before and after entrance exams. Anxiety was more closely related to the increased risk of having TMD, with 62% and 61% of students with TMD symptoms evidencing anxiety at the beginning and end of course respectively (de Lucena et al., 2012) .

Individuals with muscles and joint pain, along with a history of degenerative joint disorder, have significantly higher levels of depression compared to those with a single condition demonstrated by Reissmann and colleagues (Reissmann et al., 2008). Cioffi and colleagues also found that individuals with a combination of chronic TMD myofascial pain and migraine were experiencing significantly higher levels of depression compared to isolated TMD groups (Cioffi et al., 2014).

A positive association between BMS, poor sleep quality and comorbid anxiety / depression on HADS was observed by Lopez-Jornet and colleagues, with every 1 point increase in HADs depression score, the odds of sleep quality deterioration increased 1.26 times (Lopez-Jornet et al., 2015) Komiyama and colleagues compared patients with BMS and TN. The authors found that pain levels were higher in TN than BMS. However, regression analysis indicated the associated risk of depression in BMS patient was significantly higher than in TN patients (Komiyama et al., 2012) . Patients with BMS and atypical odontalgia (AO) were studied by Takenoshita and colleagues to investigate psychiatric diagnosis in COFP patients.

The authors observed depressive tendencies in 32.1% of BMS patients and 33.3% of individuals with AO (Takenoshita et al., 2010). Gerrits and colleagues focused on body pain areas and the onset of anxiety and/or depression, observed that pain specifically in orofacial region was associated with depression symptoms (Gerrits et al., 2014).

McMillan and colleagues study indicated that patients with OFP were 3.5 times more likely to exhibit moderate to severe depression compared to control participants and also OFP pain individuals with widespread pain symptoms demonstrated more psychological distress (McMillan et al., 2010).

A prospective study by Macfarlane and colleagues of OFP in young adults identified a strong association between adult life events and increased of OFP with psychological distress. Depressive symptoms were identified in 35.1% of individuals, with an associated risk more than double that of healthy controls (OR = 2.18) (Macfarlane et al., 2009).

2.1.5. Discussion

Chronic orofacial pain is prevalent, disabling in nature and requires biopsychosocial approach for holistic management (Ghurye and McMillan, 2017). Concomitant anxiety and depression symptoms commonly occur with chronic pain. This is a review of 43 studies on psychological factors (anxiety and/or depression) in OFP conditions. The review identified positive associations between pain intensity, duration, chronicity and symptom severity and the presence of anxiety / depression. Anxiety in neuropathic pain conditions ranged from 36.7% to 54.3% of cases and depression from 25.7% to 76.7% of cases. Moderate to severe depression was observed in 15.5% of individuals and moderate to severe anxiety was in 33.7% of individuals with neuropathic pain. Anxiety in non-neuropathic pain conditions ranged from 34.4% to 62.0% of cases and depression from 26.0% to 76.9% of cases. Moderate to severe

depression was observed in 19.5% to 53% of cases with non-neuropathic pain and moderate to severe anxiety in 24.5% of cases. TMD pain (muscular) had stronger associations with anxiety than depression

Cancer phobia was identified both in BMS and TMD patients, this was linearly related to heart disease phobia. Gender differences demonstrated that both anxiety and depression are strongly associated with females rather than males or at least in TMD pain, females are at greater risk of anxiety and depression than males. Across studies individuals with multiple OFP conditions were more likely to have severe negative psychological impairment, most obviously high levels of depression, compared to those with a single condition.

There was a substantial degree of variability in the study design of the selected articles for this review, each having their own biases, which contributed to the difficulty in arriving at a consensus. Five studies used a longitudinal prospective design (de Lucena et al., 2012, Fillingim et al., 2013, Macfarlane et al., 2009, Kindler et al., 2012, Gerrits et al., 2014), three were case control (Schmitter et al., 2010, Kim et al., 2010, Gustin et al., 2011), five were retrospective (Reiter et al., 2015, Dougall et al., 2012, Porto et al., 2011, Bertoli et al., 2007, Sevrain et al., 2016) studies. Eight studies (Lee et al., 2008, Gustin et al., 2011, Castro et al., 2008, Davis et al., 2014, Stavrianos et al., 2009, Nifosi et al., 2007, Sevrain et al., 2016, Mladenovic et al., 2014) were with relatively small sample size. The true effect detection is reduced when the sample size is small (Button et al., 2013). Most of the studies (33) were cross sectional studies (Smith et al., 2013, Lee et al., 2008, Manfredini et al., 2010b, Cioffi et al., 2014, Celic et al., 2011, Ozdemir-Karatas et al., 2013, Kotiranta et al., 2015, Komiyama et al., 2014, Komiyama et al., 2012, Wan et al., 2012, Manfredini et al., 2010a, Rodrigues et al., 2012, Licini et al., 2009, Burris et al., 2009, Reissmann et al., 2008, Buljan et al., 2008, de Souza et al., 2012, Lopez-Jornet et al., 2015, Guarda-Nardini et al., 2012, Pesqueira et al., 2010, McMillan et al., 2010, GaldOn et al., 2006, Xu et al., 2011, Castro et al., 2008, Davis et

al., 2014, Stavrianos et al., 2009, Nifosi et al., 2007, Bakhtiari et al., 2010, Macianskyte et al., 2011, Takenoshita et al., 2010, Mladenovic et al., 2014, Giannakopoulos et al., 2010) where the data was collected at single point in time. The majority of studies were conducted at tertiary care units through opportunity sampling. Patient recruitment from a tertiary care unit may not be representative of general population, reducing generalizability and external validity of the study. This may have resulted in over presentation of anxiety / depression. In cross sectional studies it is difficult to differentiate between cause and effect through simple association (Mann, 2003). From this review a clear association on the aetiological pathway could not be established, if pain resulted in psychological morbidity or vice versa.

There was significant variation in the use of psychological tools for data collection. Various self-reported questionnaires were used. This may have affected the validity of the data due to variation in personal characteristics, levels of patients' intelligence, their ethnicity, culture and social beliefs (Del Boca and Noll, 2000). The majority of studies in the current review using only a single psychological scale. OFP research remained focused on TMD pain. Commonly used tool was RDC/TMD Axis II, specifically intended for and validated in TMD pain patients. The second most frequently used scale was Hospital Anxiety and Depression Scale (HADS); designed by Zigmond and Snaith. HADS depression scores varies depending upon the region it is administered, this puts validity and generalisability of the scale in question (Cameron et al., 2011). HADS in chronic pain studies has demonstrated satisfactory sensitivity for anxiety and depression evaluation, but for anxiety and depression diagnosis, does not show good specificity (Castro et al., 2006). Symptom checklist-90-Revised (SCL-90-R) has shown to be an adequate screening tool for chronic pain patients (Hardt et al., 2000) and widely used by various studies. It is considered as a multidimensional instrument (Derogatis and Cleary, 1977). However, some subscale discriminant validity is questionable, especially in chronic pain patients (Hardt et al., 2000). More research is needed through a

standardised set of questionnaires, screening and addressing wider psychological and social aspects.

There are some specific issues related to diagnosis of COFP in that there are several classification systems that do not entirely concur with each other, therefore results are not completely comparable. Literature on orofacial pain classification have discussed this issue in detail (Renton et al., 2012b, Klasser et al., 2018) emphasising the need for a standardized biopsychosocial classification of OFP and is also highlighted in this review.

The review identified a close association between COFP and psychological comorbidities. This is in line with available literature where psychological factors are now recognised as important comorbid features in presentation of OFP (Renton et al., 2012b, Smith et al., 2013). All types of pain are influenced by psychological components; however, persistent and chronic pains appear to have a wider component (Okeson, 2008, Vickers and Boocock, 2005). COFP has a profound influence on psychological health of individuals; this include anxiety, stress / worry / phobias, depressive symptoms, catastrophizing and emotional disturbances, (Ohrbach and Durham, 2017) including oral health related quality of life (Shueb et al., 2015a). Increased pain intensity negatively impacts quality of life (Haviv et al., 2017).The American Psychiatric Association (APA) have recognised that mental disorders such as anxiety disorders, somatoform disorders and mood disorders are closely related to medical conditions including pain perception.(Okeson, 2008)

Few studies have compared different orofacial pain conditions with respect to impact on psychological functioning. Available evidence has focussed on comparison of TMD pain with trigeminal neuropathic pain or migraine. On evaluation (anxiety and depression), mixed findings were reported. Primarily, no statistical difference for anxiety and depression among groups were found (Aggarwal et al., 2008a, Gustin et al., 2011, Cioffi et al., 2014). One study

showed that patient reported experience for neuropathic pain was more severe but TMD myofascial pain patients are more likely to have higher levels of psychological symptoms (Porto et al., 2011). This concurs with the findings of a recent systematic review reporting the frequent co-occurrence of psychiatric disorders and masticatory muscle pain (Wieckiewicz et al., 2017). The present review also highlights that individuals presenting with multiple pain conditions are more likely to have pronounced psychological impact (Dougall et al., 2012, Cioffi et al., 2014). Similar findings have been reported in OFP literature (Ballegaard et al., 2008) .

In this review, limited data sets were used and only English language articles were searched reducing the scope of reviewed studies. Due to heterogeneity of studies, meta-analyses was not possible, however, reducing the strength of the findings. Nevertheless the results are consistent with the hypothesis that orofacial pain conditions have an impact on psychological wellbeing of individuals and are meaningful in the context of formulating treatment strategies.

2.1.6. Conclusions

Orofacial pain has a significant impact on the patients' psychological wellbeing. This systematic review highlighted an association between OFP and psychological comorbidity. Due to heterogeneity across studies it was not possible to compare various studies fully in order to substantiate evidence in a robust manner. Most work involves patients with TMD pain (non-neuropathic), much less concerns other types of pain such as neurovascular, neuropathic and idiopathic OFP. Future research should focus on comparing psychological morbidity in different types of COFP. There is also a need for studies exploring pre condition psychological morbidity that may have a role in predisposing individuals to develop chronic pain (Macrae, 2008, Dersh et al., 2002).

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Paper 2

Psychological impact of patients with neuropathic, musculoskeletal and neurovascular orofacial pain

2.2. Psychological impact of patients with neuropathic, musculoskeletal and neurovascular orofacial pain

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Statement of Clinical Relevance

Chronic orofacial pain causes psychosocial dysfunction. Its management requires a biopsychosocial approach. Assessment of various aspects of psycho-social functioning of individuals with chronic orofacial pain is important. Within non-neuropathic pain group, patients with neurovascular conditions contributed most to the high scores. This highlights that neurovascular pain patients as a sub group may require more intense psychological input.

2.2.1. Abstract

Introduction: Orofacial pain (OFP) is an unpleasant sensation in the area of the face. It is commonly prevalent and produces significant level of disability and distress. Management of orofacial pain is complex and requires a multidisciplinary approach **Aims:** This study aims to evaluate the psychological impact of chronic orofacial pain (COFP) through existing standardised questionnaires and to assess the contribution of psychological function of neuropathic, musculoskeletal (TMD), neurovascular orofacial pain using standardised questionnaires incorporated in (IMPARTS) Integrating Mental and Physical healthcare: Research, Training and Services. **Methodology**: Patients between the ages of 18-80 years were recruited from the OFP clinic at King's College Hospital London. Their demographic details were noted, and psychological questionnaires were administered. According to their responses, the psychological impact of OFP was assessed. **Results:** A total of 319 patients were recruited. Two hundred and thirty five (73.6%) patients were females and 84(26.3%) were males. Mean age was 48.98 years (age range from 20-80 years). Psychological questionnaires were filled by 189 (59.2%) patients. Almost 40% of individuals did not complete the questionnaires for reasons such as; questionnaires lost in the post, few individuals refuse to complete and others reported that questionnaire set was lengthy and tedious. Neuropathic pain; (Post traumatic neuropathic pain was identified in 149 (46.7%) cases, trigeminal neuralgia in 20 (6.2%), burning mouth syndrome in 6 (1.8%) cases). Temporomandibular disorders pain (TMD); were reported by 112 (35.1%) cases. Neurovascular pain; (migraine was identified in 44 (13.7%) cases, headache in 34 (10.6%) cases, trigeminal autonomic cephalalgia in 9 (2.80%) cases). Dysfunctional pain; (Persistent idiopathic facial pain was identified in 4 (1.20%) case). Possible anxiety disorder was in 34%

of neuropathic cases, 31.7% in TMD group and 53.3% in neurovascular group. Possible depressive symptoms for neuropathic pain group was identified in 36.80% of cases, for TMD, in 23.10% of cases and for neurovascular in 42.60% of cases. On follow up visit improvement scores were 1.10 (SD 1.9) for neuropathic pain, 1.56 (SD 2.5) for TMD group and -.5(SD 4.2) for neurovascular group. Coping mean scores were 5.7(SD 2.9) for neuropathic pain. For TMD mean scores were 6.7 (SD 2.5) and for neurovascular group it was 5.9 (SD 3.1). **Discussion:** The findings of this study have shown that in the neuropathic pain group, despite scoring lower on pain severity and visual analogue scale (VAS) scores, the functional impairments and oral health impact profile scores were high. However, the overall quality of life and some psychological indicators such as depression, anxiety and post-traumatic stress were less pronounced compared to the neurovascular pain group. The non-neuropathic neurovascular group has higher pain severity as indicated by VAS scores. But less pronounced effect on oral health impact, however, more prominent impact on general quality of life and other psychological indicators (e.g. anxiety, depression and post-traumatic stress). No statistical significant difference among groups were seen in terms of psychological measures. However, neurovascular patients as a subgroup tended to evidence scores, indicative of greater psychological dysfunction and reduced quality of life. On understanding diagnosis p=0.001 and outcome coping p=0.03, showing statistical significance. **Conclusion:** The study concluded that chronic orofacial pain patients are influenced negatively psychologically. Neurovascular group is highlighted as a subgroup that may require increased and or intense psychological input.

2.2.2. Introduction

Orofacial pain is a noxious, painful experience in the region of the face and /or oral cavity (IASP, 2016). Pain is multifaceted and there is a significant degree of subjectivity to the pain experience (Coghill, 2010), which includes both the central and the peripheral nervous systems, influenced by multiple pain modulating factors such as past painful experience, cognitive components and the emotional state of an individual (Alencar, 2013, Wiech et al., 2008). There is wide ranging variability amongst individual's pain experience (Renton et al., 2012b). Females to male ratio being 1:2 (Shinal and Fillingim, 2007). Pain sensitivity is also linked to cultural differences (Al-Harthy et al., 2016). Age, psychological state of mind (Carlson, 2007) and presence of chronic painful conditions are associated with pain experience (Macfarlane et al., 2004).

Chronic pain continues for more than 3 – 6 months (Merskey and Bogduk, 1994b) and produces a significant degree of impairment among individuals which result in excessive use of healthcare resource (Breivik et al., 2013, Leadley et al., 2012). Persistent OFP consultation cost due to multiple specialities involvement is identified as the major healthcare utilization, cost (Durham et al., 2016) compared to other dental patients (Aggarwal et al., 2008b). There is increased work day loss (Shueb et al., 2015a), and considerable impact on oral health related quality of life of an individual (Shueb et al., 2015a). A strong link between long standing orofacial pain and depression and anxiety symptoms is evident in the literature. With impaired psychological function, there is a change in beliefs and cognitions (Nilsson et al., 2013).

Global burden of disease (GBD) is measured through years lived with disability (YLD) and is calculated through disease prevalence and its severity. The GBD study identified chronic pain conditions in the top ten causes of YLD in every country. Anxiety and depression were associated comorbidity with chronic pain and were also considered in the top ten causes of

YLD in every country (Rice et al., 2016). This is a recognised public health problem (Institute of Medicine Committee on Advancing Pain Research, 2011, Goldberg and McGee, 2011, Gallagher and Verma, 1999) and requires a biopsychosocial approach for holistic management (Cheatle, 2016).

For psychological assessment of patients with pain, emotional states and emotional processing mechanism of an individual needs to be considered (Lumley et al., 2011). Family interactions and various life experiences, affect coping abilities of an individual (Jamison and Edwards, 2012). It is important to measure psychosocial impact of such individuals to be able to have an understanding of their perspective and to provide tailored made treatment in line with stratified medicine. Earlier studies, mostly have used a single questionnaire to assess the psychological state of an individual with chronic OFP and usually the focus was on one or two types of OFP and not the full spectrum. Gustin et al, (Gustin et al., 2011), Macianskyte et al (Macianskyte et al., 2011) and Castro et al (Castro et al., 2008) investigated 2 types of OFP. Single questionnaire cannot be used to assess the extent of the psychological and behavioural component (Demetriou et al., 2015) and may result in identifying false positive responses (Hersen, 2004). This study aims to explore the psychological functioning and its impact of various orofacial pain types, using multiple questionnaires which cover a wide range of psychological problems.

2.2.3. Methods

This was a prospective study, evaluating patience attending specialist orofacial pain clinic at King's College Hospital, London. The **Inclusion criteria** were participants aged 18 to 80 years. Individuals with good understanding of the English Language, both written and verbal and presenting with chronic orofacial pain that was started spontaneously, after an accident or

following a medical or dental procedure. **Exclusion Criteria** were; individuals with dental or gum pain, individuals with a history of a pre-existing psychological condition requiring active treatment with psychotropic medications, which can alter pain perception and individual's performance as per study protocol. Individuals participating in other concurrent studies and with learning disability. The patients were assessed during the first consultation and were excluded if they do not fulfil the inclusion criteria.

2.2.3.1. Consent

Patients were provided with an information sheet detailing the project. This was followed by verbal explanations. Once the patient agreed to consent, they signed the consent form.

All the collected information remains confidential. Clinicians and other members of research team will abide by Data Protection Act. All staff involved have undergone formal training in Good Clinical Practice.

2.2.3.2. Ethical approval

National Research Ethics Service committee London Dulwich, record reference number is 15/L0/1108. The project identification is Integrated Research Application System (IRAS) number 173208, dated 22/07/2015. A copy is attached as appendix 1.

2.2.3.3. Data Collection

Data was collected from February 2016 to October 2016. (Questionnaire set is attached in appendix 4). An Excel spread sheet was populated for data collection. This was transferred to Statistical Package for the Social Sciences (SPSS Version 22) for calculations.

Before the consultation, patients were provided with a set of standardised questionnaires for psychological analysis of OFP. This includes, Euroqol-5 Dimensions,

General Anxiety Disorder-7, Patient Health Questionnaire-9, Multidimensional State of Perceived Social Support, Oral Health Impact Profile-14, Chronic Pain Acceptance Questionnaire, Short Form McGill Pain Questionnaire-2, Pain Detect, Pain Catastrophizing Scale and Pain Self-Efficacy Questionnaire.

Clinical examination of the patients was performed by calibrated trained clinicians after they completed above mentioned set of questionnaires. OFP diagnosis was made on the basis of International Headache Society Classification for OFP (ICHD-3, 2013), Diagnostic Criteria for Temporomandibular Disorders (Schiffman et al., 2014) and International Association for the Study of Pain (IASP, 2011). (Diagnostic coding sheet is attached as appendix 3)

Patient description of pain with any associated autonomic symptoms, difficulty in daily functioning and concomitant medical conditions were also recorded.

At follow up appointment, a record was made on outcome of management. This included both improvement in symptomatology or worsening of condition and improvements in their coping with chronic pain, using patient reported outcome measure scale (PROMS) (Devlin and Appleby, 2010). Attached as appendix 5.

2.2.3.4. Sample Size Determination and Statistical Analysis

For sample size calculation, comparisons across diagnostic groups are complicated to a degree by the presence of multiple diagnoses for individual patients. Nevertheless, assuming twice as many patients present with ‘neuropathy only’ than ‘TMD only’ (based on the historical pattern of referred patients’ diagnoses at the clinic), then to detect a functional difference of half a standard deviation ($d = 0.5$) with significance level of 0.05, the required sample size to achieve an 80% power ($\beta=0.2$) can be determined by $n = 96$ for ‘neuropathy only’ and $n = 48$ for ‘TMD

only'. It is also anticipated that the sample size will be sufficient for determining any improvement in patients' pain over the course of treatment. Assuming a baseline mean pain intensity in orofacial pain patients of 4 (out of 10) with standard deviation of 2.5 (Gustin et al., 2011, Smith et al., 2013), to detect a meaningful decrease in pain (i.e., 30%; (Farrar et al., 2001) with significance level of 0.05, the required sample size to achieve an 80% power (β=0.2) can be determined by n = 36.

Scaled responses (from questionnaires) were analysed descriptively for patients, with overall means, and standard deviations (SD) reported. The proportion of patients scoring above pre-defined cut-offs for neuropathic pain (PainDETECT), depression (PHQ-9) and anxiety (GAD-7) measures was calculated. Diagnostic groups were compared across measures using one-way analysis of variance (ANOVA) for continuous measures where distributions were approximately normal (skewness/kurtosis range between –1.5 and +1.5; (Hair et al., 1998) or non-parametric equivalent (e.g., Kruskal-Wallis test) where significant skew or kurtosis was present, and using chi-squared tests for categorical measures. Changes in values between time points for continuous measures of treatment outcome (e.g., pain outcome) were measured using paired sample t-test or non-parametric equivalent (according to data distribution).

2.2.4. Results

2.2.4.1. Prospective data; demographics and reported conditions

A total of 319 patients' data was collected prospectively. Two hundred and thirty five were females (73.6%) and 84 were males (26.3%). The mean age was 48.98 years with standard deviation of ±14.1 (range was from 20 years to 80 years).

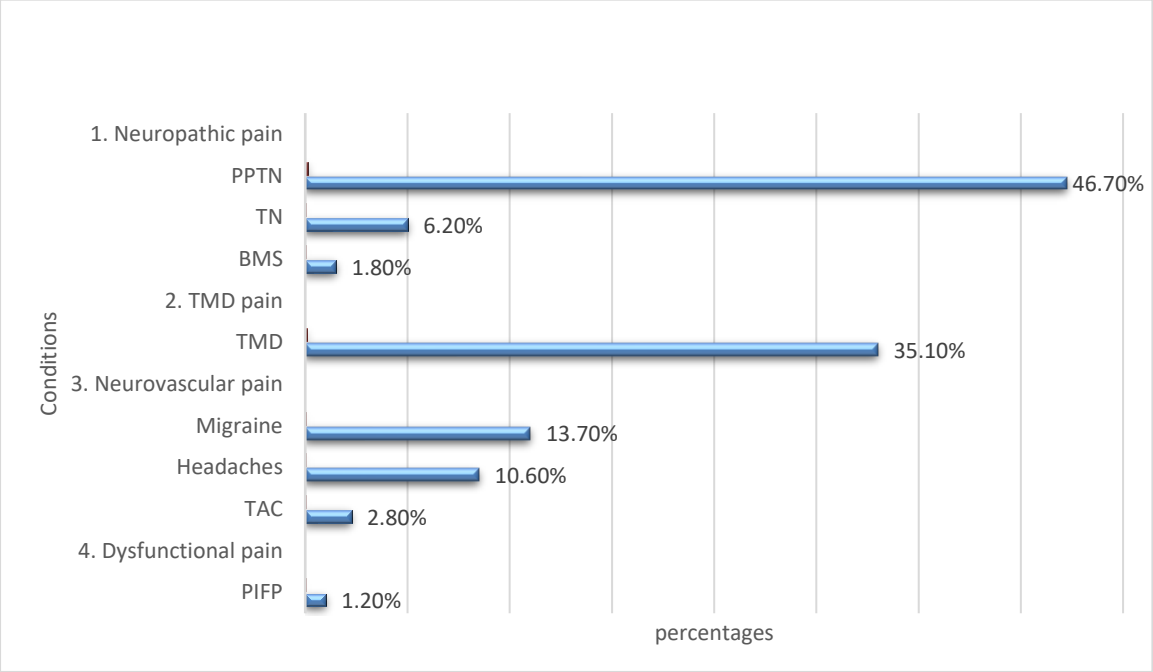
Seventy-four (23.1%) were white British, 13 (4.0%) were Asians, 9 (2.8%) were European, 19 (5.9%) were Black British and 3 (0.94%) were Hispanic. Two hundred and one

(63%) did not identify themselves as belonging to any ethnic group and were classified as non-specified.

An average duration of the problem was 39 months (SD 56.7) (range was 1 – 420) and mean VAS score was 4.9 (SD 3.1).

2.2.4.2. Diagnosed orofacial pain Conditions

Painful post traumatic neuropathic pain (PPTN) was in 149 (46.7%) cases and Temporomandibular disorders (TMD) were in 112 (35.1%) cases. Figure 1 shows the percentages of various diagnosed OFP conditions.



Conditions diagnosed by the clinicians

Some of the patients had more than one condition as a result it is not possible to sum up the total percentage to 100. BMS (burning mouth syndrome), TN (trigeminal neuralgia), PPTN (painful post-traumatic trigeminal nerve injury), TMD (temporomandibular disorders), TAC (trigeminal autonomic cephalalgia), PIFP (persistent idiopathic facial pain

Figure 2.2.1 Diagnosed conditions

Chronic OFP patients were grouped together on broad symptomatic classes i.e. neuropathic, musculoskeletal, neurovascular and idiopathic (Benoliel and Sharav, 2010). For

Neuropathic pain**,** mean age was 50.9 years (SD 14.3), mean duration of pain was 29.2 months (SD 48.4) and mean VAS was 4.3 (SD 3.2). For Temporomandibular Disorders pain (TMD), mean age was 46.9 years (SD 14.4), mean duration of pain was 44.5 months (SD 61.1) and mean VAS was 5.3 (SD 2.6). And for Neurovascular pain Mean age was 46.9 years (SD 14.9), mean duration of pain was 41.2 months (SD 41) and mean VAS 5.3 (SD 2.7).

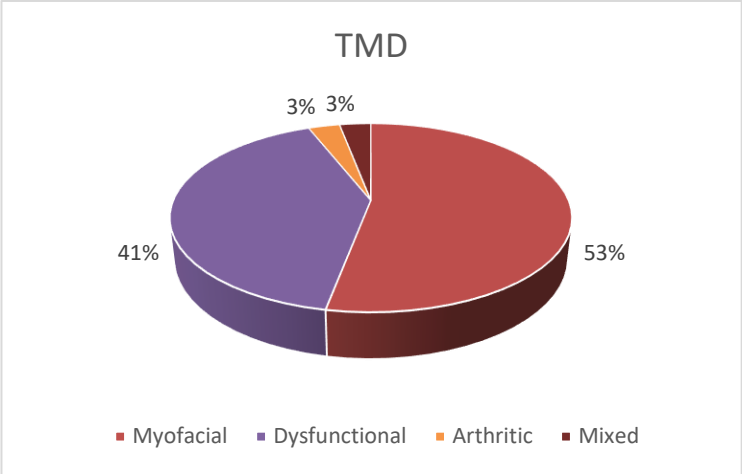
Proportion of reporting sides and sites of pain by the patient is shown in table 1.

Table 2.2.1. Reported sides and sites proportions of OFP

Reported percentages of sides and sites for OFP		
Side		
Left 121(37.90%)	Right 118(36.90%)	Bilateral 78(24.40%)
Site		
V1 (Ophthalmic nerve; First branch of Trigeminal nerve) 58(18.10%)	V 2 (Maxillary nerve; Second branch of Trigeminal nerve) 128(40.10%)	V3 (Mandibular nerve; Third branch of Trigeminal nerve) 120(37.60%)
		V3Lingual (Lingual branch of mandibular nerve) 28(8.70%)

One hundred and twelve (35.10%) individuals reported temporomandibular disorders (TMD). Proportions of various categories of TMD are shown in Figure 2.

There were 17 (15.10%) of individuals, who had TMD along with comorbid headaches. Evidence suggest that headaches occur concomitantly with temporomandibular disorder and other body pain conditions, influencing quality of life negatively (Nixdorf et al., 2008).

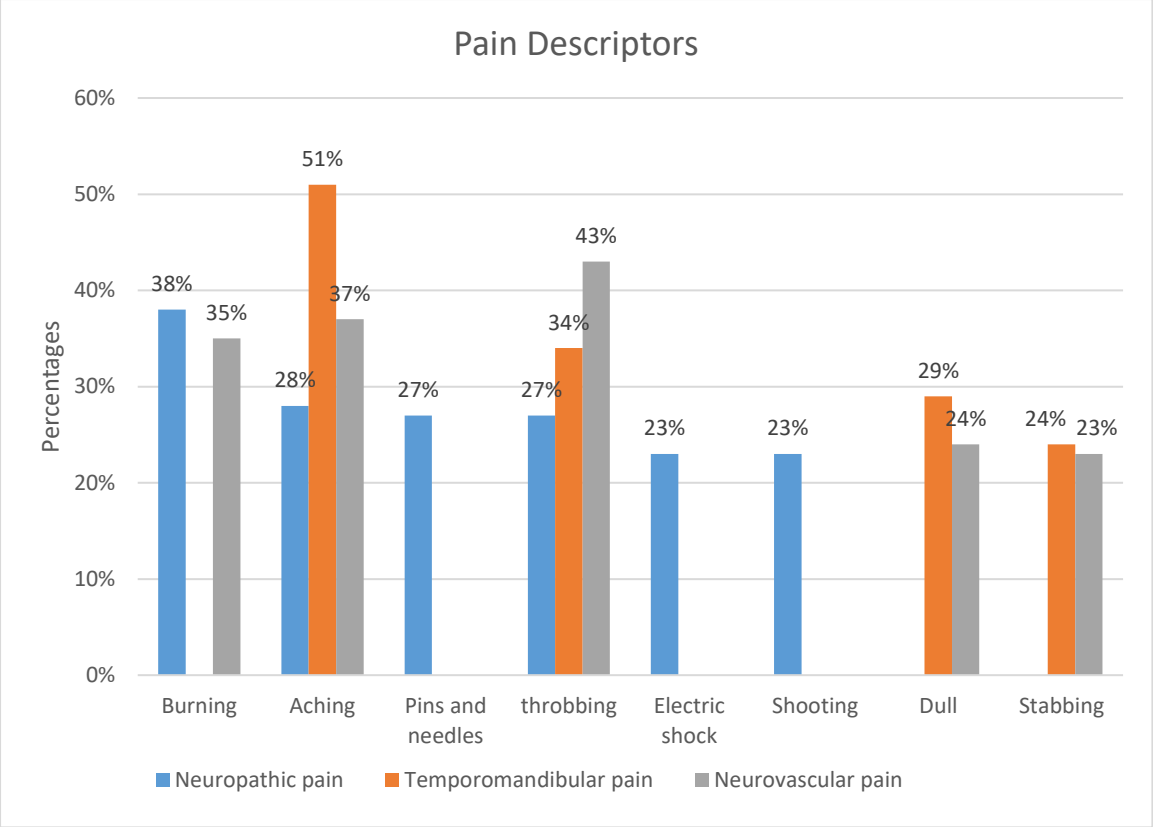


Percentages of various temporomandibular disorders (TMD)

Figure 2.2.2 Various TMD pain percentages

2.2.4.3. Pain descriptors

Common descriptors used by the patients to express pain are shown in Figure 3. Non-neuropathic group had mostly used aching and throbbing to express their discomfort, whereas neuropathic group used burning relatively frequently.



Report of pain descriptors in patients with neuropathy, TMD and neurovascular pain

Figure 2.2.3 Pain descriptors

COFP patients experience various daily functioning impairments. The percentages of patients in each diagnostic group reporting problems in daily function is shown in table 2. A greater proportion of patients with neuropathic pain tended to report problems such as difficulties with eating, teeth brushing, speech and kissing compared to TMD and neurovascular pain groups, who generally were highly comparable across functional domains'.

2.2.4.4. Functional impairment

Table 2.2.2. Reported Functional impairments across groups

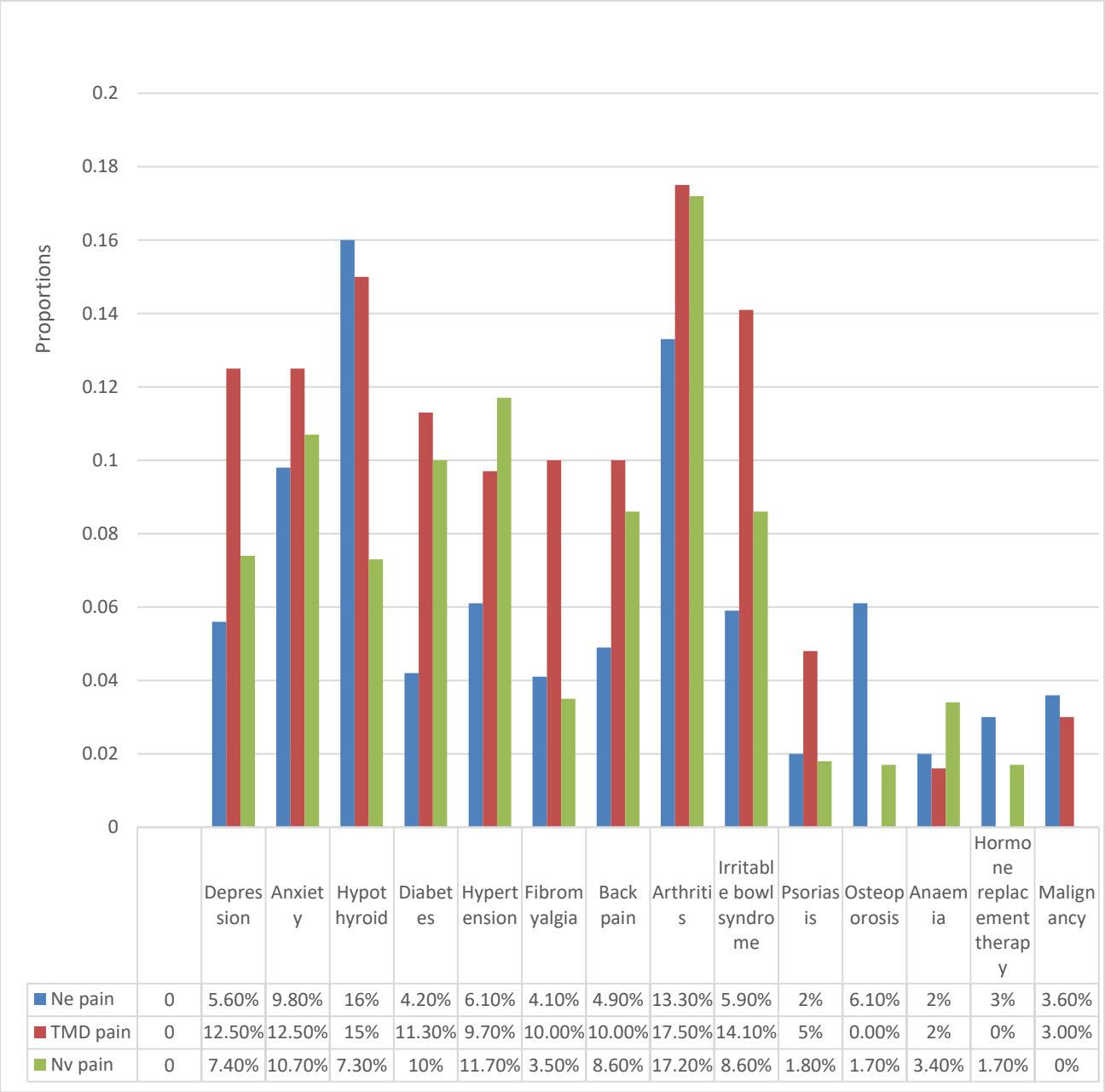
	Neuropathic pain only	**TMD pain only (Non-neuropathic)**	**Neurovascular pain only (Non-neuropathic)**	**P Value**
Problem with eating	41 (47.7%)	22 (61.1%)	1 (5.3%)	P<0.001
Problem with teeth brushing	24 (33.3%)	3 (15%)	1 (6.3%)	P=0.038
Problem with speech	22 (27.2%)	2 (7.4%)	2 (10.5%)	P=0.045
Problem with sleeping	17 (22.4%)	8 (26.6%)	3 (15.0%)	P=0.623
Problem with taste	9 (15%)	0(0.00%)	0 (0.00%)	P=0.060
Problem with kissing	11 (14.9%)	0 (0.00%)	0 (0.00%)	P=0.032
Problem with socialising	8 (14.0%)	3 (13.6%)	3 (17.6%)	P=0.924
Problem with work	8 (13.3%)	0 (0.00%)	0 (0.00%)	P=0.073
Problem with pronunciation	7 (12.5%)	1 (5.6%)	2 (11.1%)	P=0.712
Problem with face washing	7 (11.7%)	1 (5.3%)	0 (0.00%)	P=0.281
Problem tongue biting	7 (11.7%)	0 (0.00%)	0 (0.00%)	P=0.117
Problem daily functioning	7 (10.1%)	2 (7.4%)	2 (10.5%)	P=0.908
Problem with mood	6 (10.3%)	1 (5%)	4 (22.2%)	P=0.229
Problem with concentration	5 (8.3%)	1 (5 %)	6 (33.3%)	P=0.010
Problem with confidence	5 (8.6%)	3 (14.3%)	1 (5.9%)	P=0.644
Problem saliva dribbles	4 (5.7%)	0 (0.00%)	0 (0.00%)	P=0.280
Problem with drinking	4 (5.7%)	1 (4%)	0 (0.00%)	P=0.565
Problem with make-up application	4 (7%)	0 (0.00%)	0 (0.00%)	P=0.287
Problem with shaving	4 (7%)	1 (5.3%)	0 (0.00%)	P=0.549
Problem lip biting	4 (6.9%)	0 (0.00%)	0 (0.00%)	P=0.294
Problem with smell	1 (1.8%)	0 (0.00%)	0 (0.00%)	P=0.727

2.2.4.5. Comorbid medical conditions

Medical conditions such as low back pain, fibromyalgia, irritable bowel syndrome are commonly associated with COFP (Stohler, 2001). Our patient cohort also reported the following concomitant comorbid medical problems, listed in table 3. Neuropathic pain group tended to had more hypothyroid, whereas non-neuropathic group had more arthritis, hypertension and irritable bowel syndrome.

Table 2.2.3. Co-Medical conditions reported by the patients

Co-Medical conditions reported by the patients		
Arthritis 25(7.8%)	Hypothyroid 23 (7.2%)	Back Pain 15 (4.7%)
Anxiety 15(4.7%)	Irritable Bowel Syndrome 14 (4.3%)	Depression 14(4.3%)
Hypertension 12(3.7%)	Diabetes 11 (3.4%)	Fibromyalgia 10 (3.1%)
Osteoporosis 6 (2%)	Malignancy 6 (2%)	Psoriasis 5 (1.5%)
Gastric reflux 5(1.5%)	Anaemia 4 (1.2%)	Hiatus hernia 3 (1%)
Hormone replacement therapy 3 (1%)	Obsessive compulsive disorder 3(1%)	Rheumatoid arthritis 2(0.6%)
Generalized body aches 2(0.6%)	Gout 2 (0.6%)	Sjogren 's syndrome 2(0.6%)
Scoliosis 2(0.6%)	Hyperthyroid 2(0.6%)	Peripheral neuropathy finger tips 2(0.6%)
Sciatica 2(0.6%)	Panic disorder 2(0.6%)	Asthma 2(0.6%)
Stress 1(0.3%)	Ulcerative colitis 1(0.3%)	Chronic Fatigue Syndrome 1(0.3%)
IgA Deficiency 1(0.3%)	Bi lateral sub dural haematoma 1(0.3%)	Raynaud's syndrome 1(0.3%)
Epilepsy 1(0.3%)	Goitre 1(0.3%)	Barret oesophagus 1(0.3%)
Gilbert syndrome 1(0.3%)	Rosacea 1(0.3%)	Ehler's-danlos syndrome 1(0.3%)
Seizures 1 (0.3%)	Dystonia 1(0.3%)	Hypermobility 1(0.3%)
Post herpetic neuralgia of thigh 1(0.3%)	Congenital retinitis pigmentosa 1(0.3%)	Chronic central pain syndrome 1(0.3%)
G6PD deficient 1(0.3%)	Lichen planus 1(0.3%)	Spinal pain 1(0.3%)
Discoid lupus erythematosus 1(0.3%)	Cyst in the brain 1(0.3%)	Fe deficient 1(0.3%)
Endometriosis 1(0.3%)	Tinnitus 1(0.3%)	Oesophageal reflux 1(0.3%)
Systemic hypermobility syndrome 1(0.3%)	Idiopathic erythrocytosis 1(0.3%)	Atrial septum aneurysm 1(0.3%)
Neck shoulder pain 1 (0.3%)	Epilepsy petit mal 1(0.3%)	
Pelvic pain 1(0.3%)	Spina bifida 1(0.3%)	Degenerative disc 1(0.3%)
Angina 1(0.3%)	Mini stroke 1(0.3%)	Multiple sclerosis 1(0.3%)



		Depression	Anxiety	Hypothyroid	Diabetes	Hypertension	Fibromyalgia	Back pain	Arthritis	Irritable bowl syndrome	Psoriasis	Osteoporosis	Anaemia	Hormone replacement therapy	Malignancy
Ne pain	0	5.60%	9.80%	16%	4.20%	6.10%	4.10%	4.90%	13.30%	5.90%	2%	6.10%	2%	3%	3.60%
TMD pain	0	12.50%	12.50%	15%	11.30%	9.70%	10.00%	10.00%	17.50%	14.10%	5%	0.00%	2%	0%	3.00%
Nv pain	0	7.40%	10.70%	7.30%	10%	11.70%	3.50%	8.60%	17.20%	8.60%	1.80%	1.70%	3.40%	1.70%	0%

Concomitant co-medical conditions reported by chronic OFP patients (Ne - neuropathic, TMD - temporomandibular disorders, Nv - neurovascular)

Figure 2.2.4 Concomitant co-medical conditions

2.2.4.6. Psychological questionnaires

One hundred and eighty-nine (59.2%) participants out of the 319 completed psychological questionnaires. All OFP groups scored low on quality of life measures. The neurovascular group in particular had extremely poor quality of life. The scores of various questionnaires for neuropathic and non-neuropathic pain groups are shown in table 4.

Table 2.2.4. Questionnaires scores for neuropathic and non-neuropathic pain

Psychological functions and quality of life

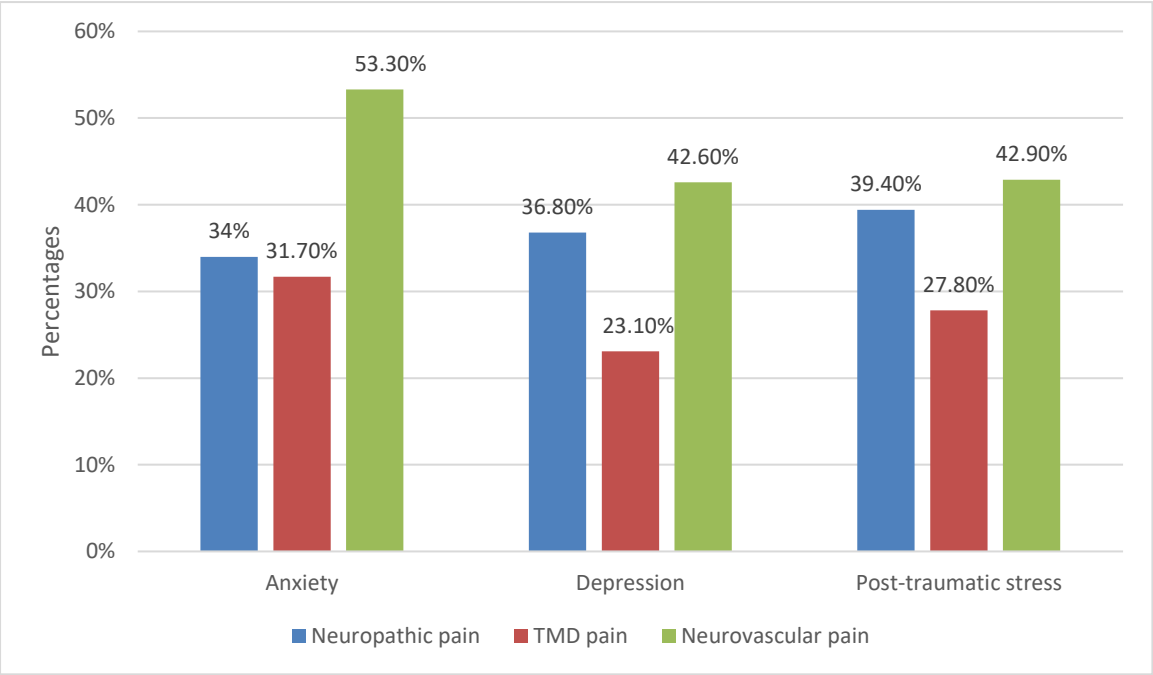
	Neuropathic pain only	**TMD pain only (Non-neuropathic)**	**Neurovascular pain only (Non-neuropathic)**	**P value**
EuroQol (Mean score) Health (-0.59-1.00)	.65 (SD .25)	.62 (SD .27)	.45 (SD .35)	P=0.039
GAD-7 (Mean score) (0-21) (≥8 probable anxiety)	5.9 (SD 6.01)	6.2 (SD 6.25)	9.2 (SD 6.6)	P=0.152
PHQ -9 (Mean score) (0-27) (≥10 moderate / severe depression)	4.7 (SD 6.4)	3.4 (SD 5.5)	7.5 (SD 8.3)	P=0.261
MSPSS (Mean score)	66.0 (SD 21.4)	63.7 (SD 21.8)	63.6 (SD 15.9)	P=0.405
OHIP-14 (Mean score) Severity (0-56)	27.2 (SD 15.0)	20.4 (SD 14.8)	23.1 (SD 17.4)	P=0.057
PCL (Mean score) (5-30)	12.8 (SD 6.8)	10.6 (SD 6.6)	13.3 (SD 8.5)	P=0.180
CPAQ (Mean score) (0-48)	27.1 (SD 9.5)	24.1 (SD 7.9)	22.6 (SD 8.9)	P=0.366
SFMPQ **Continuous** **Intermittent** **Neuropathic** **Affective**	 2.4 SD(2.6) 2.3 SD (3.0) 2.3 SD (2.4) 2.3 SD (2.9)	 2.8 SD(2.6) 2.8 SD (2.7) 1.5 SD (1.8) 1.9 SD (2.5)	 3.1 (SD 2.4) 2.3 (SD 2.4) 2.5 (SD 2.7) 1.8 (SD 2.5)	 P=0.639 P=0.700 P=0.30 P=0.70
PainDETECT (Mean score)	17.0 (SD 9.3)	12.3 (SD 9.3)	8.6 (SD 6.2)	P=0.014
PCS (Mean score) (0-52)	19.3 (SD 15.5)	17.3 (SD 18.1)	21.2 (SD 15.5)	P=0.657
PSEQ (Mean score) (0-60)	30.8 (SD 19.0)	27.2 (SD 22.3)	21.1 (SD 16.6)	P=0.28
Note: For cut off values of relevant questionnaire see appendix 4.2				

Neuropathic pain group GAD scale, showed mild anxiety in 18 (19.1%) of cases. Moderate in 11(11.7%) cases and severe anxiety in 13 (13.8%) cases. In the TMD group mild anxiety was in 10 (24.4%) cases, moderate in 6 (14.6%) and severe anxiety in 5 (12.2%) of cases. In the neurovascular group, mild anxiety was in 3 (20%) cases, moderate anxiety in 5 (33.3%) of cases and severe anxiety was in 3 (20%) cases. Overall, possible anxiety disorder was in 34% of neuropathic cases, 31.7% in TMD group and 53.3% in neurovascular group.

On the PHQ scale, mild depression was observed in 17 (18.9%) individuals of neuropathic pain patients, 4 (10.3%) of TMD pain patients and 3 (25%) of neurovascular pain group. Moderate depression was identified in 5 (5.6%) of neuropathic group, 2 (5.1%) of TMD group patients and in 1 (8.3%) individual of neurovascular group. Moderately severe depression was identified in 5 (5.6%) of cases of neuropathic pain, 2 (5.1%) of TMD and 2 (6.7%) of neurovascular group. Severe depression was in 6 (6.7%) of neuropathic pain group, in 1 (2.6%) of TMD pain and in 1 (8.3%) case of neurovascular pain.

On PCL, post-traumatic stress was identified in 37(39.4%) of neuropathic pain group, in 10 (27.8%) of the TMD group and in 6 (42.9%) of neurovascular pain individuals.

Figure 5, shows graphic presentation for anxiety, depression and post-traumatic stress across three groups of patients.



Psychological burden for each group

Figure 2.2.5 Psychological Burden

2.2.4.7. Outcome 1 after 1st consultation

The outcome questionnaire was completed by 174 patients with the aim to assess their comprehension of their condition and their satisfaction with the consultation. Due to small number of individuals identified in each non-neuropathic pain subgroup (TMD + Neurovascular pain), these were merged together for analysis purpose.

Table 2.2.5. Outcome 1

Outcome after first consultation				
	Neuropathic pain only	**TMD pain only**	**Neurovascular pain only**	**P Value**
Pain scores **(0-4)** **(5-9)** **(10)**	 7(7.6%) 36(39.1%) 49(53.3%)	 3(15.8%) 20(48.8%) 4 (21.2%)	 4(9.8%) 7(46.7%) 5(33.3%)	P=0.36
Satisfaction score (0-4)	6 (6.6%) 18 (19.8%)	3(7.7%) 12(13.8%)	1(6.7%) 3(20%)	P=0.710

(5-9) **(10)**	67 (73.6%)	24(61.5%)	11(73.3%)	
Understanding Diagnosis **Mean score** **(N)**	8.40 (SD 2.7) (92)	8.17(SD 2.9) (41)	7.40(SD 3.6) (15)	P<0.001
Note: scores for understanding diagnosis/satisfaction range from 0-10.				

The average pain scores of the whole sample after first consultation were: 0-4, was reported by 10.7% of individuals. Pain scores, 5-9 was reported by 44.4% of individuals and 10 was reported by 44.9% of individuals. This suggests that at baseline, 44.9% were in extreme pain (score 10), whereas 44.4% were experiencing high levels of pain and discomfort (score 5-9) and only 10.7% reported mild pain (score 0-4).

The average pain score of 10 (extreme pain) was observed in 53.3% of neuropathic pain patients on their first appointment, a score of 5-9 (higher levels of pain) was in 39.1% of individuals and a score of 0-4 (low levels of pain) in 7.6% of individuals. Among non-neuropathic pain patients (TMD + Neurovascular), score of 10 (extreme pain) was experienced by 54.5% of individuals, a score of 5-9 (higher levels of pain) by 95.5% and score of 0-4 (low levels of pain) in 25.6% of individuals.

2.2.4.8. Satisfaction scores

After the first consultation, 73.6% of patients with neuropathic pain, were extremely satisfied (score 10) with their consultation, 19.8% were in the range of moderate to high levels (score 5-9) of satisfaction and 6.6% were in the low range (score 0-4) of satisfaction. Satisfaction mean scores in non-neuropathic pain group (TMD + Neurovascular) (n=54) were: scores 0-4 were in the low range of satisfaction in 7.4% (4) of cases, scores 5-9 moderate to high levels of satisfaction in 27.7% (15) of cases, score 10 in 63.2% (12) of cases. For the whole sample, 69.0% of the total pain group individuals were extremely satisfied (score 10) with their

consultation, 23.4% of individuals were in the range of moderate to high levels of satisfaction (score 5-9) and 7.6% were in low range (score 0-4) of satisfaction levels.

2.2.4.9. The patients' understanding of their diagnosis

Patients' understanding of their diagnosis after the first consultation by 49.1% (92) of individuals in the neuropathic pain group, mean score was 8.40 SD (2.7) and for non-neuropathic TMD pain patients, was 8.17 SD (2.9) by 21.9% (41) of individuals. For neurovascular pain patients the mean score was 7.40 SD (3.6) by 8.0% (15) of individuals.

This indicated that neuropathic pain individuals have a relatively good understanding of their condition compare to non-neuropathic pain group.

2.2.4.10. Outcome 2

One hundred and thirteen patients attended the follow up visit. The table 6, shows the scores of 81 patients with only one OFP condition for the purpose of comparison.

Table 2.2.6. Outcome 2 Improvement scores

Outcome 2 Patient self-reported improvement in pain condition scores on follow-up visit

Outcome 2 follow up visit				
	Neuropathic pain only **N=52**	**TMD pain only (Non-neuropathic)** **N=25**	**Neurovascular only (Non-neuropathic)** **N=4**	**P value**
Pain scores **Average** **Worst** **Lowest**	Mean (SD) 4.3(SD 2.7) 6.2(SD 3.4) 2.7(SD 2.5)	Mean (SD) 4.3 (SD 2.9) 6.7 (SD 3.5) 2.8 (SD 2.3)	Mean (SD) 5.48 (SD 2.7) 7.5 (SD 3.1) 3.5 (SD 2.4)	
Improvement score	1.10 (SD 1.9)	1.56 (SD 2.5)	-.50 (SD 4.2)	P=0.554
Coping score	5.7 (SD 2.9)	6.1 (SD 2.8)	5.9 (SD 3.1)	P=0.03

For the neuropathic pain patients the mean improvement score was 1.10 SD (1.9) reported by 52 (46%) of individuals. For non-neuropathic TMD pain, the mean improvement

score was 1.56 SD (2.8), reported by (25)22.1% of individuals. For neurovascular pain the mean improvement score was -.50 SD (4.2) reported by 3.5% (4) of individuals.

Comparison of pain level assessment at first and at follow-up visit of a whole sample through the paired sample t test for average pain, the mean difference score value reported was 0.017 (SD 2.7) with 95% CI (-.84 to.63) and p= 0.773, indicating a non-significant difference between the two assessment periods. For worst pain, the reported mean score difference was -1.79 SD (4.17), with 95% CI (-1.2 to 0.93) and p value was P= 0.75, indicating that the mean difference is not statistically significant. For lower pain, the reported pain difference was 0.31 SD (2.58), with 95% CI (-1 to 0.36) and p=0.35, indicating no statistical significance between the mean difference of the two assessment periods.

For neuropathic pain group, mean coping score of 0-4 were in 19 (26.9%) cases, 5-9 score were in 44 (62%) and 10 score were in the 8 (11.3%). In non-neuropathic TMD pain, the mean coping score of 0-4 were in 9 (19.6%), 5-9 score were reported by 33 (71.7%) and 10 score were reported in 4 (8.7%) cases. In non- neuropathic (neurovascular pain) pain group, mean coping scores of 0-4 were in 8 (26.7%) cases, 5-9 scores were in 11 (56.3%) cases and score 10 were in 5 (16.7%).

2.4.5. Discussion

Orofacial pain is not a condition with single aetiology, due to its heterogeneous pathologies in the region of face, mouth, head and neck (Macfarlane et al., 2001). The complicated anatomy of this region together with the possibility of various confounding factors makes the definitive diagnosis a difficult process (Zakrzewska, 2013b). Chronic orofacial pain is related to significant disability and patients with this pain are no different than patients with chronic pain

of other parts of the body in context of gender differences, psychological distress, pain intensities and comorbid psychological disorders (Turner and Dworkin, 2004).

Management of chronic orofacial pain is a challenge for clinicians and can easily result in misdiagnosis. Koopman et al investigated diagnosis validation on facial neuralgia and idiopathic facial pain and found that on validation of diagnosis by pain experts, almost 48% of cases were wrongly diagnosed by primary care physicians (Zakrzewska, 2013b). This is equally confusing and tiring for the patients as well since they need to visit numerous healthcare professionals prior to receiving adequate pain diagnosis and subsequent management (Zakrzewska, 2013b)

Screening of psychological functioning was performed using multiple self-reported questionnaires for the present study. This is to cover various aspects of psychological impact of chronic orofacial pain on individuals. So far, in the literature previously performed studies have not covered such a wide range of orofacial pain and have not used multiple questionnaires to assess various aspects of psycho-social functioning of individuals with chronic orofacial pain. The study selected validated questionnaires for data collection instead of interviews to yield usable good quality (Williams, 2003) information from large number of individuals in a cost effective manner and also numerical analysis can describe the observation in a meaningful way (Jack and Clarke, 1998).

In the current study, female to male ratio was a 2.7:1. This is comparable to other studies that have shown that more females are effected by orofacial pain compared to males. Shinal et al reported a female to male ratio of 2:1 (Shinal and Fillingim, 2007) and Cioffi et al in a study had female to male ratio of 3.1:1(Cioffi et al., 2014). This variability may be due to innate differences of both the genders in perceiving somatic and visceral symptoms and difference in expression (Barsky et al., 2001).

The study sample observed 34% of the individuals of the neuropathic pain group exhibited features of anxiety, in 36.8% of cases reported depression and 39.4% of cases reported symptoms of post-traumatic stress disorder. In non-neuropathic pain group, neurovascular pain scored higher for anxiety 53.3%, depression 42.60% and PTSD 42.90%. Zwart et al found a direct association between anxiety, depression and migraine with a stronger association for anxiety disorder (Zwart et al., 2003). For the neuropathic pain group, our findings were in line with the Smith and colleagues study on nerve injury patients (Smith et al., 2013) in the same settings. However, psychosocial function has not been compared across neurovascular, neuropathic and musculoskeletal groups previously.

Post-traumatic stress in orofacial pain is common (Sherman et al., 2005). Pain and affective distress of chronic orofacial pain conditions accentuates the presentation (Sherman et al., 2005). Burris and colleague investigated PTSD symptoms in neuropathic and non-neuropathic (TMD) pain, PTSD symptoms were reported by 23% of cases and were significantly associated with increased pain intensity (r=0.37), increased symptoms of psychological (r=0.71) and affective distress (r=0.51). PTSD symptoms were significantly associated with depression (r=0.64) and anxiety (r=0.67) (Burris et al., 2009).

Significant functional disabilities were identified across groups. However, some differences were identified. The neurovascular pain group scored high on concentration and mood problems compared to the neuropathic group or TMD group. The neuropathic pain group were more likely to report difficulties with eating, teeth brushing and sleeping. Available evidence suggest psychiatric comorbidities such as anxiety, depression and mood disorders in migraine patients (Antonaci et al., 2011) and functional problems with nerve injury patients (Renton et al., 2012a).

The findings of this study were also consistent with the study by Yazdi et al, who have observed high levels of anxiety and depression in orofacial pain patients with significant interference in their daily life (Yazdi et al., 2012). However, Yazdi and colleagues reported only on nerve injury patients.

The burden of orofacial pain on quality of life was measured through EuroQol-5D-5L. The health evaluation mean score for neuropathic pain was 0.65 (SD .25) and for non-neuropathic, TMD only group was 0.62 (SD .27), for neurovascular only group it was 0.46 (SD .35). It illustrates significantly less pronounce health quality than the normal healthy UK population on EQ-5D-5L, the range was 0.93 to 0.80 (Kind et al., 1999). The neurovascular group's health related quality of life was significantly reduced compared to the neuropathic group.

Chronic OFP influences oral health related quality of life of individuals. This is shown by our study. The measured mean values for this study were significantly above the OHIP mean value 5.1 (CI 4.8 – 5.3) of the UK dentate population (Slade et al., 2005).

Catastrophizing is maladaptive cognition (King, 2002), and an irrational negative forecast of the future (Quartana et al., 2009). The scores of this study indicated pain catastrophizing in our sample and were significantly higher as reported in a PCS validation study on community sample, the reported mean was 13.9 (Osman et al., 2000). In the present study, there was more pain catastrophizing in non-neuropathic neurovascular group compared to neuropathic group. This may be due to extreme pain experience as demonstrated by VAS scores.

Comorbid medical conditions such as Paget's disease, metastatic disease, hyperthyroidism, multiple myeloma, hyper-Parathyroid, vitamin B, folic acid, iron deficiency, systematic lupus erythematosus, and Cancer chemotherapy were associated with COFP and

headaches (Renton, 2017). This study also reported on co-existing medical conditions like back pain in 4.7% of cases, fibromyalgia in 3.1% of cases, hypothyroid in 7.2%, irritable bowel syndrome in 4.3%, hypertension in 3.7% and malignancy in 2% of cases of COFP patients. Scientific Literature have highlighted presence of co-medical problems such as fibromyalgia (Alpaslan, 2015), low back pain, irritable bowel syndrome, sleep disturbance and headache (Hoffmann et al., 2011, Yunus, 2008) in COFP patients. Individuals with pre-existing psychological conditions were excluded from our study because such individuals can either have diminished or elevated pain perception (Papežová et al., 2005, Sakson-Obada, 2017).

Review of patients on follow up visit in this study had shown improvement in coping scores in all groups. TMD pain group coped slightly better whereas, Castro and colleague observed trigeminal neuralgia patients coped better than TMD (Castro et al., 2008). This may have been due to psycho-education given to the patients in the first consultation. It is assumed that this process would have given them better understanding and clarity of their condition. This would help individuals to cope better. Evidence also suggests that psychological interventions such as cognitive behaviour therapy (Matsuoka et al., 2017) and mindfulness (Merrill and Goodman, 2016) facilitate to skilfully respond to our bodily sensations and improve coping skills.

In order to manage pain, it is important to measure pain quality, duration, intensity and its impact on quality of life (Renton et al., 2012). This enables a clinician to have a better differential diagnosis. Once the diagnosis is obtained, a management strategy can be delivered against these parameters (Renton et al., 2012). Medical research has improved our understanding of both physical and psychological functions related to chronic pain. This may facilitate in developing management plans to improve individual's physical health, aid recovery and to minimise their psychological burden even if pain is not fully relieved.

This study has highlighted that patients with chronic orofacial pain have significant degree of co- morbid psychological conditions such as anxiety, depression and post-traumatic stress disorder.

Study limitations

The study did not include patients with more than one type of pain in the analysis and no comparison was made among patients with comorbid conditions i.e. neuropathic pain + neurovascular pain. Which is one of the main limitation and this may be addressed in future projects. Self-reporting questionnaires were used for this study and a positive association was found between pain intensity/chronicity with mood symptoms. This illustrated a significant correlation between the two although it is not possible to clearly demonstrate if one is dependent on the other or vice versa. Psychological state of mind influences perception of pain in individuals (Geisser et al., 2000) and may influence their responses to self-reporting questionnaire.

There was no clear distinction in neuropathic and non-neuropathic group on psychological measures. Within non-neuropathic pain group patients with neurovascular conditions contributed most to the high scores. This highlights that neurovascular pain patients as a sub group may require more intense psychological input. The study also showed that multidisciplinary input from psychology and neurology in the management contributed to improvement in symptom reduction and coping skills.

2.4.6. Conclusion

Presence of persistent pain raises fear and anxiety in individuals and these emotions negatively influence pain experience. This study compared psychological impact of neuropathic and non-

neuropathic orofacial pain conditions and showed that the neurovascular pain group as a subgroup requiring more psychological support compared to neuropathic and/or TMD pain groups. Pain has both sensory and emotional components. The biomedical approach of management only treats one component of this condition. The emotional component management requires a psychosocial approach as highlighted by medical research. This therefore requires a comprehensive assessment, including assessment of psychological component if one aims to fully manage the problem and promote recovery. Future research is needed to compare individuals with two or more pain types and use of qualitative / mixed methodology to ascertain the extent of this problem.

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Paper 3

Changing face of orofacial pain: The diagnostic impact of working with Neurology on an orofacial pain clinic

2.3. Changing face of orofacial pain: The diagnostic impact of working with Neurology on an orofacial pain clinic

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2.3.1. Abstract

This study assessed the impact of collaborative working with a headache neurologist on diagnoses of patients attending orofacial pain (OFP) clinic. Patient diagnostic data was collected from adult patients attending an Orofacial Pain Service from January 2013 to January 2017. A liaison headache neurologist was appointed late 2015; OFP clinics were co-run with the neurologist specialist thereafter. Overall, 639 patients attended the service; 315 in 2013-2015 and 324 in 2016-2017. Compared to 2013-2015, there were increased rates of diagnoses related to neurovascular (27.5% vs. 19.0%; *P*= .012) and musculoskeletal pain (36.9% vs. 26.0%; *P*=.003) in the 2016-2017 cohort and decreased rates of neuropathic (55.6% vs 70.2%; *P*<.001) and atypical/idiopathic pain (1.3% vs. 5.4%; *P*=.003) diagnoses. There was a trend towards an increased rate of comorbid diagnoses (26.3% vs. 20.3%; *P*=.077), especially those relating to headache conditions. The findings suggest that introduction of a specialist headache neurologist into the OFP clinic widened its remit of assessment, increasing recognition of (co-morbid) neurovascular-related pain and decreasing atypical / idiopathic pain diagnoses in patients with complex OFP. The increase rate of musculoskeletal pain diagnosis in the later cohort is likely attributable to service expansion and normalisation of diagnostics reportedly seen in other OFP services.

Statement of Clinical relevance: Orofacial pain is a complex diagnosis, it requires a multidisciplinary approach that includes neurological input.

Key words: Orofacial pain, misdiagnosis, post traumatic neuropathic pain, temporomandibular disorder, idiopathic facial pain, headache, neurovascular.

2.3.2. Introduction

Misdiagnosis of orofacial pain and poor pain management are one of the most common causes of patient complaints related to dentistry (GDC forum data 2016) (Simmons, 2017). Dentists are familiar with odontogenic pain, however, non-odontogenic pain can mimic toothache leading to misdiagnosis and inappropriate management (Balasubramaniam et al., 2011).

Orofacial pain OFP classifications are multiple and conflicting, they include; International Classification of Headache Disorders (ICHD-3β)[(ICHD-3, 2013)] (which include headache or facial pain caused by disorders of the teeth in Chapter 11 and the other non-dental causes of OFP are included in Chapter 13) (ICHD-3, 2013), the International Association for the Study of Pain (IASP) (Merskey and Bogduk, 1994b) classification (which has been modified to acknowledge peripheral and centralised driven pain), the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD)(Schiffman et al., 2014) and the American Academy of Orofacial pain(Klasser et al., 2017). The lack of a consensus in diagnostic criteria may lead to increased misdiagnosis of OFP (Woda et al., 2005).

The numerous causes of OFP reflect the complex anatomical boundaries involved and give rise to diagnostic and management challenges for OFP conditions, which require clinical input from multiple specialities. Multidisciplinary approaches to diagnosis and management of OFP has proven to be cost effective strategy for managing OFP and complex headache disorders (Turk, 2002). The orofacial pain service at Kings College Hospital, London consults a high volume of OFP patients (>1000 per year) including follow-up visits. Initially, the OFP service relied entirely on dental specialities with referral to other specialities without direct liaison with neurology. By 2013, clinical psychology and liaison psychiatry were introduced to OFP service. Due to recognition of multiple medical and pain co-morbidities in patients seen on the OFP service in 2015, a liaison headache neurologist was appointed to the Multidisciplinary Team (MDT) to improve diagnostic process and management of a range of orofacial pain

conditions. In addition to assessing patients with (possible) neurovascular conditions, the neurologist facilitated staff training in headache clinical presentation through observations of the specialist assessing patients, MDT team discussions with neurology input, and an increased emphasis on identifying migraine-headache associated symptoms when assessing patients presenting with OFP. In this service evaluation study, we evaluated the impact on an existing OFP service of working with a specialist headache neurologist on OFP diagnosis.

2.3.3. Methods

The study sample included consecutive patients, aged 18 years and above, attending the OFP Clinic at King's College London Hospital from January 2013 to January 2017. The service from 2013 was run by a multidisciplinary pain team including; oral surgery, oral medicine, clinical psychology and liaison psychiatry, the only newly introduced member (neurology) was in early 2016. A need for neurological input was identified due to the medical complexity of multiple OFP diagnostics. This coincided with a newly appointed academic lead for neurology with headache interest to the main trust hospital in early 2016. In 2016 the service became established with increase referrals (from approximately 1800 to 2500 appointments per year), from other centres. The primary analyses compared the diagnoses given to patients attending the OFP Clinic at King's College London Hospital before and after the appointment of a headache Neurologist.

2.3.3.1. Clinical examination and diagnosis

Clinical examination of the patients was performed by trained clinicians in the OFP. A diagnosis or diagnoses (in the case of multiple conditions associated with orofacial pain) was/were made according to the International Headache Society Classification (ICHD-3, 2013), the Research Diagnostic Criteria for Temporomandibular Disorders (Dworkin and

LeResche, 1992) and the International Association for the Study of pain (Merskey and Bogduk, 1994a). The clinics were co-run with the neurologist specialist. Initial assessment was conducted by the oral surgeon and depending on the outcome - if it was indicated that a patient required assessments by a neurologist - then this was asked for.

2.3.3.2. Data collection

For patients referred to the clinic from January 2013- December 2015, patients' case notes were retrospectively analysed. In addition to demographic data, relevant information about diagnosis and condition history (duration) was extrapolated from case notes. Data for patients referred to the clinic from January 2016 – January 2017 was collected prospectively and included demographic, diagnosis and condition history. Patients were recruited in accordance with approval by the local Trust Research and Development Committee. Ethical approval for the study was provided by the National Research Ethics Service Committee, London Dulwich (REC number 15/L0/1108). Informed consent was taken from the individual participants for their anonymized data to be used for research purposes.

2.3.3.3. Data Analysis

Descriptive data was presented in the form of mean, standard deviation (SD), absolute number and percentage (%). Comparisons of demographic variables between 2013-2015 and 2016-2017 cohorts were performed using independent group *t*-tests with bias-corrected and accelerated [2000 repetitions] bootstrapping methods employed where continuous distributions violated normality assumptions. Differential diagnosis rates, grouped together based on broad symptomatic classes (neuropathic, musculoskeletal, neurovascular and idiopathic (Benoliel and Sharav, 2010)) were compared between cohorts using chi-square tests, with odds ratios (OR) and 95% confidence intervals (CIs) calculated. The level of significance was set at $P <$ 0·05. All statistical analyses were completed with the SPSS, version 24.

2.3.4. Results

Over the study period, 639 consecutive adult patients presenting with orofacial pain attended the clinic as a result of referrals from general practice or other specialist dental services; 315 in the 2013-2015 cohort and 324 in the 2016-2017 cohort. The majority of patients were female (464 or 73.0%) with no differences between groups (2013-2015 73.4%; 2016-2017 72.5%; *P* = 0.806). The mean age was a little under 50 years (Mean (M) = 48.17, SD = 14.26) and the age distribution was highly comparable between cohorts (2013-2015 M = 48.11, SD = 14.35; 2016-2017 M = 48.23, SD = 14.19; *P* = 0.917). The median duration of pain onset was 18.0 months (inter-quartile range (IQR) = 7.0-48.0) with 93.1% of patients reporting pain for 3 or more months at clinic appointment. Time since pain onset was similar in both cohorts (2013-2015 Median = 16.0, IQR = 7.0-36.0; 2016-2017 Median = 18.0, IQR = 7.0-48.0; *P* = 0.577).

2.3.4.1. Orofacial pain diagnoses

Data concerning patient diagnosis was examined for all cohort patients. Where patients in the 2016-2017 cohort had a provisional diagnosis only (17 or 5.2%), this was used. At the time of data collection, 4 (1.2%) patients in the 2016-2017 cohort had received neither a formal diagnosis nor a provisional diagnosis due to ongoing investigations – these patients were excluded from subsequent descriptive and comparative analyses. Almost 30% of 2016-2017 patients (92 of 320) with a diagnosis had been referred to specialist headache neurologists for examination after consultation with oral surgery staff members.

In total, 148 (23.3%) patients presented with multiple diagnoses. A fifth of (64 or 20.3%) patients in the 2013-2015 cohort had multiple diagnoses (2 diagnoses *n* = 55, 3 diagnoses *n* = 9). This increased to more than a quarter (84 or 26.3%) in the 2016 cohort (2 diagnoses *n* = 69, 3 diagnoses *n* = 13, 4 diagnoses *n* = 2), a difference that was marginally significant ($\chi 2 = 3.13$, *P* = 0.077).

Table 2.3.1. Patients' diagnosis presenting with OFP in 2013-2015 & 2016-2017 cohort

Diagnoses for patients presenting with orofacial pain in 2013-2015 and 2016-2017 cohorts.

	2013-2015 (*n* = 315)	2016-2017 (*n* = 320)
	***n* (%)**	***n* (%)**
Neuropathic		
Painful Post Traumatic Neuropathy	151 (47.9)	98 (30.6)
Persistent Dento-Alveolar Pain 2	0 (0.0)	29 (9.1)
Spontaneous Neuropathy	26 (8.3)	20 (6.3)
Persistent Dento-Alveolar Pain 1	4 (1.3)	2 (0.6)
Burning mouth syndrome	8 (2.5)	11 (3.4)
Trigeminal Neuralgia Classical	17 (5.4)	15 (4.7)
Trigeminal Neuralgia Non-classical	19 (6.0)	6 (1.9)
Occipital Neuralgia	0 (0.0)	8 (2.5)
Geniculate Neuralgia	0 (0.0)	1 (0.3)
Musculoskeletal (Temporomandibular Disorders)		
TMJ Myofascial Pain of the Masticatory muscles	52 (16.5)	66 (20.6)
TMJ Arthritis/Arthalgia	3 (1.0)	3 (0.9)
TMJ Disc Displacement with/without reduction	26 (8.3)	45 (14.1)
TMJ Mixed (Muscular and Joint diseases)	1 (0.3)	4 (1.3)
Neurovascular (Headache disorders)		
Trigeminal Autonomic Cephalalgia		
Unspecified	3 (1.0)	2 (0.6)
Cluster Headaches	0 (0.0)	1 (0.3)
SUNCT	3 (1.0)	4 (1.3)
SUNA	1 (0.3)	0 (0.0)
Paroxysmal Hemicrania	2 (0.6)	2 (0.6)
Hemicrania Continua	0 (0.0)	9 (2.8)
Migraine		
Head Migraine	25 (7.9)	42 (13.1)
Facial Migraine	12 (3.8)	7 (2.2)
Other Primary/Secondary Headaches	17 (5.4)	40 (12.5)
Atypical/Idiopathic		
Persistent Idiopathic Facial Pain	13 (4.1)	5 (1.6)
Atypical Odontalgia	4 (1.3)	0 (0.0)
Neurological		
Facial Dystonia	1 (0.3)	0 (0.0)

Notes: Diagnoses are not mutually exclusive across patients (64 and 84 patients had received more than one diagnosis in the 2013-2015 and 2016 cohorts, respectively) - as such, percentages in each column do not add up to 100%; TMJ = Temporomandibular Joint and Muscle Disorders; SUNCT = Short-Lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing; SUNA = Short-Lasting Unilateral Neuralgiform Headache Attacks with Cranial Autonomic Symptoms; Other Primary/Secondary Headaches includes tension-type headaches.

The frequencies (percentages) of diagnoses associated with patients' presenting orofacial pain for each cohort is displayed in Table 1. With respect to neuropathic pain conditions, there were decreases in the proportion of patients with painful post traumatic neuropathy (PPTN) and patients with spontaneous neuropathy. The most obvious change, however, was the emergence of the diagnosis of persistent dento-alveolar pain 2 (PDAP2) under PPTN. This was a reconciliation of problematic recommendations in classification guidance for PDAP where it emerged that persistent dento-alveolar pain 1 (PDAP1), considered under spontaneous neuropathy, was infrequently diagnosed in both cohorts; however PDAP 2 was considered synonymous with PPTN. The proportion of patients diagnosed with burning mouth syndrome (BMS) increased very slightly in the 2016-2017 cohort while a small number of cases of occipital neuralgia and geniculate neuralgia, absent in 2013-2015, were identified in the recent cohort.

The vast majority of TMD diagnoses were myofascial pain of the masticatory muscles or joint disc displacement (with or without reduction) and were observed more frequently in the 2016-2017 cohort of patients. Within neurovascular pain classifications, trigeminal autonomic cephalalgia (TAC) was diagnosed in a small number of cases only, although 10 patients did receive a diagnosis of hemicrania continua in the 2016-2017 cohort compared with none in the earlier cohort. However, the proportion of patients with head migraines (V1) and other primary or secondary headaches increased markedly from 2013-2015 to 2016-2017. A small number of patients were diagnosed with atypical facial pain / persistent idiopathic facial pain (PIFP); 4 patients in the early cohort were diagnosed with atypical odontalgia, a sub type of PIFP(ICHD-3, 2013), but none received this diagnosis in 2016-2017 cohort.

Table 2.3.2. Comparison of diagnostic classifications for patients in 2013-2015 and 2016-2017 cohorts according to broad symptomatic class

Comparison of diagnostic classifications for patients in 2013-2015 and 2016-2017 cohorts according to broad symptomatic class.

	2013-2015 (n = 315)	2016-2017 (n = 320)			
	n (%)	n (%)	χ^2	OR (95% CI)	P
Symptomatic Class					
Neuropathic	**221 (70.2)**	**178 (55.6)**	**14.36**	**0.53 (0.38,0.74)**	**<0.001**
Musculoskeletal (Temporomandibular Disorders)	**82 (26.0)**	**118 (36.9)**	**8.65**	**1.66 (1.18,2.33)**	**0.003**
Neurovascular (Headache Disorders)	**60 (19.0)**	**88 (27.5)**	**6.35**	**1.61 (1.11,2.34)**	**0.012**
Trigeminal Autonomic Cephalalgia	9 (2.9)	18 (5.6)	2.99	2.03 (0.90,4.58)	0.084
Migraine	37 (11.7)	46 (14.4)	0.97	1.26 (0.79,2.01)	0.326
Other Primary/Secondary headaches	**17 (5.4)**	**40 (12.5)**	**9.80**	**2.50 (1.39,4.52)**	**0.002**
Atypical/Idiopathic Pain	**17 (5.4)**	**4 (1.3)**	**8.54**	**0.22 (0.07,0.67)**	**0.003**

Notes: Classifications under symptomatic class headings are not mutually exclusive across patients (64 and 84 patients had received more than one diagnosis in the 2013-2015 and 2016 cohorts, respectively) - as such, percentages in each column do not add up to 100%; Chi-square tests were administered for comparisons; OR = odds ratio, CI = confidence interval; All significant group differences are highlighted in bold.

Formal comparisons between cohorts of differential diagnosis rates, grouped together broadly according to main symptomatic class, revealed several significant differences (Table 2). Diagnoses of neuropathic pain were less common in 2016-2017, decreasing from over 70% in 2013-2015 to under 60%. In contrast, the odds of diagnoses of TMD and of neurovascular-related conditions both increased by approximately 1.6 fold in the recent cohort. More specifically, the proportion of TAC and migraine diagnoses in the 2016-2017 cohort increased, although differences between cohorts were not significant (Table 2). When head migraines were considered separately (Table 1), there was a significant increase (7.9% in 2013-2015 to 13.1% in 2016-2017; P = 0.033), however. Most obviously, the odds of a diagnosis relating to other primary/secondary headache significantly increased by 2.5 times. Finally, there was a significant and marked decrease in the number of diagnoses associated with atypical/idiopathic pain given in 2016-2017 compared with 2013-2015.

Table 2.3.3. Patterns of diagnostic classifications

Patterns of diagnostic classifications for patients presenting with orofacial pain in 2013-2015 and 2016-2017 cohorts according to comorbidity and aetiology of condition.

	2013-2015 (n = 303)	2016-2017 (n = 315)
Diagnostic Classification	***n* (%)**	***n* (%)**
Neuropathic Only	187 (61.7)	147 (46.7)
Musculoskeletal (TMD) Only	37 (12.2)	69 (21.9)
Neurovascular Only	24 (7.9)	35 (11.1)
Neuropathic + Musculoskeletal (TMD)	19 (6.3)	11 (3.5)
Neuropathic + Neurovascular	10 (3.3)	15 (4.8)
Musculoskeletal (TMD) + Neurovascular	21 (6.9)	33 (10.5)
Neuropathic + TMD + Neurovascular	5 (1.7)	5 (1.6)

Notes: Diagnoses under the 'Atypical/Idiopathic' classification were not considered; patients with a sole diagnosis under the 'Atypical/Idiopathic' classification (e.g., persistent idiopathic facial pain) were excluded from the table and comparative analysis (2013-2015 n = 12; 2016 n = 5); A 2 (Group) x 7 (Diagnostic Classification) chi-squared test revealed a significant difference in proportions in each classification according to cohort (χ^2 = 22.08, P = 0.001); TMD = temporomandibular joint disorder.

Analyses indicated significantly higher rates of diagnoses relating to neurovascular pain in the 2016-2017 cohort compared to the 2013-2015 cohort, and a trend in the recent cohort towards patients receiving multiple diagnoses more frequently. An examination of the patterns of diagnostic rates, considering comorbid diagnoses with different symptomatic classification, reflected a marginally significant increase in rates of comorbid neurovascular and neuropathic and/or musculoskeletal (TMD) pain diagnoses in the 2016-2017 cohort (P = .080) rather than a change in comorbid neuropathic and TMD pain diagnoses, which decreased slightly (Table 3). Notably, within the 2016-2017 cohort, patients with a diagnosis of neurovascular pain were much more likely to be diagnosed with a comorbid orofacial pain condition with a different symptomatic classification (e.g., a comorbid neuropathic and/or musculoskeletal pain; 53/88 or 60.2%) than patients with a diagnosis related to neuropathic pain (31/178 or 17.4%) or a diagnosis of musculoskeletal (TMD) pain (49/118 or 41.5%).

2.3.5. Discussion

This study explored the impact of a headache neurologist in an OFP clinic, on diagnoses and treatment. Following the introduction of neurology input, we found an increase in the diagnoses of neurovascular/headache disorders, most obviously head migraine and other primary/secondary headaches, but also a trend for increased recognition of trigeminal autonomic cephalalgias (TACs). Furthermore, there was a tendency towards more comorbid (symptom classification) diagnoses, predominantly in cases where one or more headache conditions were identified. These changes cannot be explained by introduction of new clinical guidance, new diagnostic criteria or additional training (other than training in headache clinical presentation) of the core OFP service staff. Commissioning of the OFP service did not change, however service expansion was observed during the overall period, possibly explaining the increase in diagnoses of TMD and related conditions in the second cohort. The marked decrease in idiopathic diagnoses and increased neurovascular diagnoses, likely reflect additional neurological input in the second cohort, although direct causality is not claimed and differences in the distribution of clinical diagnoses may also relate to natural changes in patient presentation over time. We nevertheless suggest that OFP clinics co-run with the neurologist specialist, which facilitate joint clinic case discussions with feedback on the appropriateness of provisional diagnoses and taking more comprehensive headache history as part of routine clinical assessment (including asking questions on migraine-associated and autonomic symptoms), enable clinicians to more often identify non-dental facial pain and reduce idiopathic diagnoses.

The significant decrease in the number of diagnoses of atypical/idiopathic facial pain given in 2016-2017 (compared with 2013-2015) to negligible levels represents a positive development. The diagnosis of atypical or persistent idiopathic orofacial pain (PIFP) is made after excluding all other possible known causes (Türp, 2001), frequently made after thorough

investigation by several medical specialities and often result in inadequate treatments before PIFP is diagnosed(Forssell et al., 2015) (Türp, 2002). In the past PIFP or atypical facial pains were frequently referred to as being psychosomatic in origin (Scully and Porter, 1999, Scully, 2002, Burchiel, 2003), a label which can be distressing for a patient (Biron, 1996). The pathophysiology of PIFP largely remains a mystery; and underlying neuropathic mechanism has been suggested although the aetiology needs further exploration (Benoliel and Gaul, 2017). Although the extent to which the decrease in atypical/idiopathic facial pain diagnoses in this study is directly attributable to improved recognition of primary headache disorders with facial pain radiation and/or the education received by clinicians whilst working with a headache trained neurologist is unclear, it likely reflects the benefits of adopting an MDT approach at the assessment stage.

The trend for increased trigeminal autonomic cephalalgias (TACs) diagnoses in the later cohort is important. TACs are a group of primary headache disorders characterized by unilateral head pain that occurs in association with generally prominent ipsilateral cranial autonomic features(Benoliel, 2012). The pain related to TACs is unilateral, normally centered over the V1 territory. However, radiation of the pain in V2 and V3 is frequently reported, making the differential diagnosis with short-lasting paroxysmal OFP condition potentially challenging (VanderPluym and Richer, 2015). It is essential to distinguish between these conditions to optimize patient management.

The decrease in the proportion of neuropathic pain diagnoses in the recent cohort, and the increase in the proportion of TMD diagnoses is more difficult to explain and is unlikely to be explained by additional neurological diagnostic input. This particular department specialises in post-traumatic neuropathy and has a higher proportion of these patients compared with most orofacial pain clinics. It is likely that due to expansion and development of the MDT OFP service more patients with TMD were referred to the service impacting on the proportions of

the diagnostic range. In addition, TMDs with masseteric and temporalis pain can be referred to maxillary and mandibular molar teeth which may also complicate diagnosis (Wright, 2000).

The present study observed an increasing trend of comorbid OFP diagnoses from one (chronological-based) cohort to the other. Considering the high comorbid prevalence of headaches, this is also likely to be attributable, at least in part, to greater neurology input in the diagnostic pathway of the recent cohort. Although the presence of painful comorbidities can add to a confusing scenario, given their potential negative impact on disease progression and treatment resistance, the importance of classifying comorbid orofacial pain conditions cannot be understated (Summers, 2000) For example, while the findings here are consistent with both clinical and population-based studies reporting a high prevalence of primary headaches associated with TMD (Franco et al., 2010, Goncalves et al., 2010), there is evidence that the presence of migraine is an important factor in both the duration and intensity of TMD pain (Speciali and Dach, 2015). As such, greater awareness of headache classification criteria content by OFP clinic staff, specifically enabled by direct liaison with a trained headache neurologist, can help staff to better identify possible comorbidities and ultimately increase chance of treatment success (Costa et al., 2017).

2.3.5.1. Strengths and limitations

The sample size in this study was large and represented all adult patients presenting with orofacial pain to national orofacial pain service within a four-year period. Additionally, the two timeframes under investigation are consecutive and yielded similar numbers of patients in each cohort that were comparable with regard to age, gender and time since pain onset. There are a number of limitations, however. Firstly, the methods of data collection differed between cohorts, with retrospective extraction of data from case notes for the early cohort in contrast to the latter cohort where data was collected contemporaneously with

patients' consultations, which may introduce some inconsistencies. Secondly, although, as noted previously, the patient pathway, dental clinical staff and diagnostic criteria were consistent over the study period (other than introduction of neurological input), the clinic did expand with additional capacity to see more referrals which most commonly are TMD conditions in OFP clinics (Durham et al., 2015a). Thirdly, it is difficult to say that if patients with neurovascular disorders in the first cohort (2013-2015) were ever referred directly to neurology, and if so, what the outcome was. If they were referred and the information on the outcome of the consultation was available, it may have resulted in less differences between the two cohorts. This needs investigation in future research. Fourthly, there was a significant proportion of diagnosed post traumatic neuropathic pain cases, likely due to the clinic lead having a specialist interest in this area. This may not reflect in other clinics involved in the care of patients presenting with OFP. Finally, although the number of formal comparisons was small and almost all analyses yielding significant results did so with associated *P* values of less than 0.001, there was no correction for multiple comparisons, raising the risk of Type I errors.

Clinicians attending patients with orofacial pain conditions should ideally have additional training in headache disorders to ensure appropriate diagnoses are made. Neurological input on clinic joint case discussion and feedback on the appropriateness of the provisional diagnosis allows collegiate learning across specialties. The findings of this study suggest that increased input by staff trained in headache neurology on orofacial pain clinics is associated with a higher rate of primary headache diagnoses, including comorbid diagnoses, and a reduction in the number of diagnoses of exclusion, such as PIFP. Introduction of neurological input to an OFP service is likely to educate a team that has not undergone explicit OFP postgraduate training. Although this is a precedent set in the US training programmes (Klasser and Greene, 2007), it remains poorly established elsewhere. Indeed, specialist

training in OFP does not yet exist in the UK (Peters et al., 2015) or mainly outside the USA. This study suggests a need for improved training of the dental workforce providing this OFP service and a need for a UK based post graduate training programme in OFP.

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Compliance with Ethical Standards

Conflict of Interest:

Author A (Aalia Karamat) declares that she has no conflict of interest. Author B (Jared. G. Smith) declares that he has no conflict of interest. Author C (Giorgio Lambru) declares that he has no conflict of interest. Author D (Tara Renton) declares that she has no conflict of interest.

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Ethical approval:

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Informed consent:

Informed consent was obtained from all individual participants included in the study.

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Chapter three

Overall Project Discussion & Conclusion

3.1. Discussion

Chronic orofacial pain is fairly common health issue and impacts both the healthcare system and the individual experiencing it. The psychological component of orofacial pain is well documented in the literature. To explore it further, three different projects were undertaken. Initially, a systematic review was carried out to have a better understanding of the extent of the problem and gaps in the research. This was followed by a project focussing on psychological functioning in patients with neuropathic, musculoskeletal and neurovascular orofacial pain. Lastly, an attempt was made to identify multidisciplinary components of care for individuals with chronic orofacial pain, incorporating neurology input in tertiary care centre.

The systematic review was conducted on 43 studies on psychological factors (anxiety and/or depression) in OFP conditions. This identified positive associations between pain intensity, duration, chronicity and symptom severity and the presence of anxiety / depression. Anxiety in neuropathic pain conditions ranged from 36.7% to 54.3% of cases and depression from 25.7% to 76.7% of cases. Moderate to severe depression was observed in 15.5% of individuals and moderate to severe anxiety was in 33.7% of individuals with neuropathic pain. Anxiety in non-neuropathic pain conditions ranged from 34.4% to 62.0% of cases and depression from 26.0% to 76.9% of cases. Moderate to severe depression was observed in 19.5% to 53% of cases with non-neuropathic pain and moderate to severe anxiety in 24.5% of cases. TMD pain (muscular) had stronger associations with anxiety than depression

Studies on BMS and TMD identified cancer phobia among patients, which was linearly related to heart disease phobia. These findings concur with a Japanese study on BMS (Matsuoka et al., 2010) and also by another review article (Bala et al., 2012). Phobic anxiety in TMD was observed by Xu and colleagues (Xu et al., 2005). Gender differences

demonstrated that both anxiety and depression are strongly associated with females rather than males or at least in TMD pain, females are at greater risk of anxiety and depression than males. These findings are in line with Bagis and colleague's retrospective study, which showed similar trend though statistical significance was not reached (Bagis et al., 2012). Gender differences in orofacial pain can be explained in the context of behavioural, psychosocial, constitutional and hormonal variation though till date no compelling outcome has reached (Poveda Roda et al., 2007). Across studies, individuals with multiple OFP conditions were more likely to have severe negative psychological impairment, most obviously high levels of depression, compared to those with a single condition. This supports Gureje and colleagues findings that individuals with more than one painful conditions tend to have increased risk of anxiety and mood disorder (Gureje et al., 2008).

Previous research on the psychological impact on patients with orofacial pain mostly focused on TMD pain compared to other types of orofacial pain conditions and mostly one or two components of psychological functions were considered. The second part of the project investigated psychological functioning in patients with neuropathic, musculoskeletal and neurovascular orofacial pain. This showed that for the neuropathic pain group, despite scoring lower on pain severity and visual analogue scale score, the functional impairments and oral health impact profile scores were high. The overall quality of life and some psychological indicators such as depression, anxiety and post-traumatic stress were less pronounced compared to the neurovascular pain group. Musculoskeletal / TMD with pain group showed similar psychological function to the neuropathic group but lower oral health impact compared with neurovascular and neuropathic groups. The neurovascular pain group has higher pain severity as indicated by visual analogue scale scores but a less pronounced effect on oral health impact and a more prominent impact on general quality of life and other psychological indicators (e.g. anxiety, depression and post-traumatic stress). Among the neurological

conditions, migraine is the most disabling problem (Goadsby et al., 2002). The World Health Organisation has reported migraine as sixth globally most disabling disorder (2015), with premonitory symptoms such as feeling tired, neck stiffness and lack of concentration (Giffin et al., 2003). A review of psychiatry comorbidity in migraine demonstrated that anxiety and mood disorders are more common in chronic headaches compared to migraine (Radat and Swendsen, 2005). A study by Peres and colleagues showed that both anxiety and depression are associated with migraine, but anxiety has a more robust association (Peres et al., 2017). These findings concur with our study.

The last part of the project was about the importance of multidisciplinary care. This encompasses professionals of various disciplines working together with diverse skills, knowledge and experience to provide best possible care to the patient for their physical and psychosocial needs. This study explored the impact of a headache neurologist in an OFP clinic, on diagnoses and treatment. Following the introduction of neurology input, we found an increase in the diagnoses of neurovascular/headache disorders, most obviously head migraine and other primary/secondary headaches, but also a trend for increased recognition of trigeminal autonomic cephalalgias (TACs). Furthermore, there was a tendency towards more comorbid (symptom classification) diagnoses, predominantly in cases where one or more headache conditions were identified. The overall importance of multidisciplinary team management was observed. This is in line with the Faculty of pain medicine document on pain management guidelines UK, which also states that multi-professional and multi-disciplinary team management is the best possible way forward (CSPMS, 2015). However, the appointment of a neurologist and its cost effectiveness needed further evaluation.

Chronic pain management necessitates addressing all those factors that modulate the subjective pain experience (Beecroft et al., 2013). Facial pain patients seem more affected by psychological comorbidity compared to other pain conditions (Sipilä et al., 2013).

Patient satisfaction and experience are considered as an indicator of quality. The key elements of quality care, such as effectiveness, patient centred, timely, efficient, equitable, therapeutic relationship and safety, define the best possible care (Mendoza et al., 2011) **)** and the physician's ability to make therapeutic and empathetic relationship translates patients' experience of illness (Ha and Longnecker, 2010). Chronic pain management is difficult both for the patient and clinician as, at times, it cannot be fully cured but instead be only managed. Patient centred approach seems to be the strategy in pain management (Frantsve and Kerns, 2007) Patients belief, catastrophizing and coping skills independently influences and predicts patient outcome (Turner et al., 2000). To establish evidence based management of chronic orofacial pain, multidisciplinary approaches and biopsychosocial model of pain management are fundamental adjuncts (Shephard et al., 2014).

Challenges of this project

- Retrospective data collection took considerable time to streamline procurement of notes from medical records. Since medical notes were stored at two different sites and the research was based on one of the sites (Denmark Hill), obtaining record from the other sites was time consuming.
- Patients were seen by different clinicians as a result the quality of information available was variable. The relevant information from some of these notes were also missing.
- In order to minimise the variability in the written notes, typed letters and correspondences were accessed to ascertain the accuracy of the information.
- Prospective data was also collected from orofacial pain clinic. Collecting information single-handedly was strenuous. Completing all questionnaires on patients, especially, when Clinics ran parallel with up to four clinicians seeing patients simultaneously. This may have led to losing some of the information.

- The response rate for psychological questionnaires was a serious methodological concern. Psychological questionnaires were either posted and the patient completed them at home and brought them back on the day of initial consultation, or if they were unable to fill them at home, they were given time to do so prior to seeing the clinician. This resulted in delays to the smooth running of clinics. Some patients were in pain and found it too overwhelming and arduous to complete the forms and refused to complete the questionnaires, thus impacting the strength of our findings.

3.2. Conclusion

Chronic orofacial pain has a significant impact on the psychological wellbeing of individuals. This project identified the psychological impact of orofacial pain and showed that the neuropathic pain group has higher psychological functional impact and oral health impact profile scores in contrast to TMD pain. However, the neurovascular pain group emerged as a subgroup requiring more psychological support compared to neuropathic and/or TMD pain groups due to elevated pain levels and poor overall health ratings. It also highlights the importance of the multidisciplinary care pathway, especially input from psychology and neurology, for holistic chronic orofacial pain management. Nonetheless, there is a need for further research in this field, especially longitudinal prospective studies on the long-term management outcome.

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Appendix

Appendix 1

1.1. Systematic review search strategy

Table: I Key terms used for search of articles for a systematic review with numbers of articles retrieved with each search

S.no	*Search terms*	*Articles retrieved*
1.	Psychosocial and orofacial pain	219
2.	Psychosocial and temporomandibular joint pain/disorder	133
3.	Psychosocial and trigeminal neuralgia	3
4.	Psychosocial and trigeminal nerve injury	2
5.	Psychosocial and burning mouth syndrome	31
6.	Psychological and orofacial pain	526
7.	Psychological and temporomandibular joint pain/disorder	224
8.	Psychological and trigeminal neuralgia	82
9.	Psychological and trigeminal nerve injury	22
10.	Psychological and burning mouth syndrome	202
11.	Depression and orofacial pain	310
12.	Depression and temporomandibular joint pain/disorder	166
13.	Depression and trigeminal neuralgia	126
14.	Depression and trigeminal nerve injury	6
15.	Depression and burning mouth syndrome	67
16.	Psychiatric comorbidity and orofacial pain	8
17.	Psychiatric comorbidity and temporomandibular joint pain/disorder	9
18	Psychiatric comorbidity and trigeminal neuralgia	0
19.	Psychiatric comorbidity and trigeminal nerve injury	0
20.	Psychiatric comorbidity and burning mouth syndrome	6
21.	Post-traumatic stress disorder and orofacial pain	20
22.	Post-traumatic stress disorder and temporomandibular joint pain/disorder	12
23	Post-traumatic stress disorder and trigeminal neuralgia	2
24.	Post-traumatic stress disorder and trigeminal nerve injury	2
25.	Post-traumatic stress disorder and burning mouth syndrome	0
26.	Anxiety disorder and orofacial pain	107
27.	Anxiety disorder and temporomandibular joint pain/disorder	77
28.	Anxiety and PDAP	10
29.	Depression and PDAP	12
30.	Post-traumatic stress and PDAP	4
31.	Anxiety and depression, post-traumatic stress and atypical odontalgia	14
32.	Atypical facial pain and post-traumatic stress, anxiety and depression	167

1.2. Critique of articles: STROBE Statement - checklist of 22 items (Von Elm et al., 2007)

STROBE Checklist 22 items	(Smith et al., 2013)	(Reiter et al., 2015)	(Lee et al., 2008)	(Manfredini et al., 2010b)	(Schmitter et al., 2010)	(Cioffi et al., 2014)	(Dougall et al., 2012)	(van Seventer et al., 2011)	(Kim et al., 2010)	(de Lucena et al., 2012)	(Celic et al., 2011)	(Ozdemir-Karatas et al.,	(Kotiranta et al., 2015)	(Komiyama et al., 2014)	(Fillingim et al., 2013)	(Komiyama et al., 2012)	(Wan et al., 2012)	(Gustin et al., 2011)	(Manfredini et al., 2010a)	(Rodrigues et al., 2012)	(Licini et al., 2009)
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	±	±	+	+	+	±	+	±	+	+	±	+	+	±	+	+
5	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	+
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
9	+	+	+	+	+	-	±	+	-	+	-	+	±	+	+	±	±	+	+	±	+
10	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
12	+	+	+	+	+	±	+	+	±	+	+	+	+	+	+	+	±	+	+	+	+
13	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+	+	+	+	+	+	+	±	+	+	±	+	±	±	+
17	+	+	+	+	+	±	+	+	+	+	-	+	+	±	+	-	±	±	±	-	±
18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19	+	+	+	+	+	-	+	+	-	±	±	+	+	-	+	±	+	+	+	-	+
20	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	±	+
21	+	+	+	+	+	±	+	+	±	+	+	+	+	±	+	±	+	+	+	±	+
22	+	+	-	-	+	+	-	+	-	-	-	+	+	+	+	+	-	+	-	-	-

Continued on the next page

STROBE Checklist 22 items	(Reissmann et al., 2008)	(Bertoli et al., 2007)	(Buljan et al., 2008)	(de Souza et al., 2012)	(Lopez-Jornet et al., 2015)	(Guarda-Nardini et al., 2012)	(Pesqueira et al., 2010)	(McMillan et al., 2010)	(GaldOn et al., 2006)	(Xu et al., 2011)	(Castro et al., 2008)	(Davis et al., 2014)	(Macfarlane et al., 2009)	(Stavrianos et al., 2009)	(Nifosi et al., 2007)	(Sevrain et al., 2016)	(Bakhtiari et al., 2010)	(Maciankskyte et al., 2011)	(Kindler et al., 2012)	(Takenoshita et al., 2010)	(Giannakopoulos et al., 2010)	(Gerrits et al., 2014)
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	+	+	+
4	±	+	±	+	+	±	+	+	+	±	±	+	+	±	±	±	+	±	+	+	±	+
5	+	+	+	+	+	+	±	+	±	+	±	±	+	±	±	+	±	±	+	+	+	+
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
9	+	±	±	+	+	+	±	+	+	±	±	+	+	±	±	±	+	+	+	+	±	+
10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
12	+	+	+	±	+	+	±	+	+	+	+	+	+	±	+	±	+	+	+	+	+	+
13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	±	+	+	±	+	+
17	±	±	-	±	±	±	±	+	+	+	±	+	+	+	+	±	+	+	+	+	+	+
18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19	±	+	±	+	+	±	±	+	+	±	-	+	+	-	+	+	+	-	+	±	+	+
20	±	+	±	+	+	+	±	+	+	±	±	+	+	±	+	+	+	±	+	±	+	+
21	±	+	±	+	+	±	±	+	+	±	±	+	+	±	+	+	+	-	+	-	+	+
22	-	-	+	+	+	-	-	+	-	-	-	+	+	-	-	+	-	+	-	+	-	+
Note: + (yes items explained), - (no items not explained), ± (to some extent the items are provided)																						

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies*** (Von Elm et al., 2007)

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram

Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 2

2.1. Ethical approval

Health Research Authority

NRES Committee London - Dulwich
Health Research Authority
Skipton House
80 London Road
London
SE1 6LH
Telephone: 0207 972 2463

26 August 2015
Professor Tara Renton
Professor in Oral Surgery
King's College London
King's College London Dental Institute
Oral Surgery Department
Bessemer Road, London
SE5 9RS

Dear Professor Renton **Study title:** **Stratified medicine and technological approaches to aid diagnosis and management of chronic orofacial pain patients.**

REC reference: **15/LO/1108**
IRAS project ID: **173208**

Thank you for your letter of 19 August 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.
The further information has been considered on behalf of the Committee by the Chair.
We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published
for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Mr Ali Hussain, nrescommittee.london-dulwich@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.
Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.
Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.
Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.
Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.
For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.
Sponsors are not required to notify the Committee of approvals from host organisations Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non-registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites
NHS sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).
Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows: *Document*	*Version*	*Date*
Covering letter on headed paper [Response to REC regarding provisional ethical approval]		19 August 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Professional indemnity policy wording]		
GP/consultant information sheets or letters [Amended GP letter]	2	22 July 2015
IRAS Checklist XML [Checklist_20082015]		20 August 2015
Letter from funder [Certificate for Grunenthal Awards]		
Letter from sponsor [Professional indemnity policy schedule]		01 August 2014
Letter from statistician [Email approval from statistician]		23 April 2015
Letters of invitation to participant [Amended Patient Appointment letter]	2	22 July 2015
Non-validated questionnaire [Questionnaires for completion by patients and clinicians]	1 (appendix VI & VII)	26 May 2015
Participant consent form [Amended Consent Form for COFP study]	2	22 July 2015
Participant consent form [Amended Consent Form for Pilot COFP study]	1	22 July 2015
Participant information sheet (PIS) [Amended Patient Information Sheet COFP Study]	2	22 July 2015
Participant information sheet (PIS) [Patient Information Sheet for Pilot COFP Study]	1	22 July 2015
REC Application Form [REC_Form_03062015]		03 June 2015
Research protocol or project proposal [Amended Research Protocol]	2	22 July 2015
Summary CV for Chief Investigator (CI) [CV_Tara Renton]	1	26 May 2015
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Summary of the study protocol]	1	26 May 2015
Validated questionnaire [Psychological measure questionnaire pack]	1	26 May 2015

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/ **15/LO/1108 Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Michael Philpot

Chair

Email:nrescommittee.london-dulwich@nhs.net

Enclosures: "After ethical review – guidance for researchers" *Copy to:*

Mr Keith Brennan

David Dawson, King's College Hospital NHS Foundation Trust

2.2. Study protocol

Professor Tara Renton

Professor in Oral Surgery

Oral Surgery Department

King's College Hospital, Dental Institute

Bessemer Road,

London SE5 9RS

Tel: 0203 299 4255

Fax: 0203 299 1213

Email: Tara.renton@kcl.ac.uk

RESEARCH PROTOCOL VERSION 2 (DATED 22/07/2015)

SHORT TITLE: Stratified medicine and technological approaches to managing chronic orofacial pain patients.

TITLE: Stratified medicine and technological approaches to aid diagnosis and management of chronic orofacial pain patients.

NRES Committee London –Dulwich Ref: 15/L0/1108

Chief investigator	Professor Tara Renton
Main site	King's College London
Study Design	A prospective study
Participants	Up to 3,000 patients over 5 years
Recruitments	Patients attending the specialist Orofacial Pain Service within the Dental Institute of King's College Hospital
Inclusion criteria	Patients will have to fulfil all of the following criteria: Male or female Between 18-80 years of age, Inclusive; Good verbal and written understanding of English; and A chronic painful condition affecting the oral and/or facial regions that either started Spontaneously, or following on from dental/medical procedure or accident.
Exclusion criteria	Patients will be excluded if they have any of the following: Age of greater than 80 years; Poor understanding or fluency of English and cannot understand or follow the instructions given by investigators; Poor proficiency at completing online questionnaires.

These patients will be given hard copy versions of the questionnaires instead To complete at their consultation appointment(s);
A history of psychosis or psychological disease either
(a) Requiring on going psychoactive drugs, or

(b) That the Investigator has reason to believe will either affect the patient's neural pathways or hinder the performance of the patient with regard to the perception of pain or ability to successfully complete the tasks required of them according to the protocol;
Involvement already in another research study or recent involvement in any research prior to recruitment;
AND/OR Mental and/or learning disabilities.

BACKGROUND: Stratified medicine (also known as "personalised medicine"or"precision medicine") can be described as identifying the different strata within a disease and
The deeper understanding of the mechanisms underpinning these strata. Stratification will allow targeting of treatments to specific disease pathways, identification of treatments effective for particular groups of patients, and co-development of diagnostics to ensure the right patient gets the
Right treatment at the right time. (1) Stratified medicine, whereby pharmacological and non-pharmacological treatment is chosen according to the biological or risk characteristics shared by subgroups of patients (2) involves assessment of specific prognostic factors orbiomarkers among
The patients, which can be in the form of genomics, metabolomics, and/or proteomics, and then tailoring the treatment method according to the results of these analyses.(1) This strategy has significantly contributed to improved patient care in several fields.

Invitation to complete questionnaires

We understand that you are likely to be suffering from oral and/or facial pain and you have an appointment within the specialist orofacial pain clinics at King's College Hospital Dental Institute.

We invite you to complete the following survey as part of your clinical assessment.

Your results may also contribute to our pilot study that will assess the use of an online survey in correctly diagnosing your condition.

Why should I complete these questionnaires?

Completing the questionnaires will enable us to identify what treatment you need

Through research, this will help us improve the outcome of your oral/facial pain condition and your overall quality of life

All data collected is anonymized and stored in a secure environment

We need your consent to use your information for research purposes in order to help improve care of patients like you in the future.

Although some of the questions may seem repetitive, please do answer all of the questions as your answers will provide us with essential information about your condition

There is a 'save and continue later' option within the survey that will allow you to answer the questions at different times - you do not need to complete the questionnaires all at once.

You can also review your answers at any time.

2.3. Patient Information sheet

The next couple of pages is the 'Patient Information Sheet' for this study (Ref: 15/LO/1108, Version 1, Dated 22/07/2015). It contains information about what will happen to the data collected and the data protection policy.

The Head of the group for this project is Professor Tara Renton, who may be contacted at tara.renton@kcl.ac.uk if you have any further questions. Alternatively you may contact the Study Coordinator, Dr Zehra Yilmaz at zehra.yilmaz@kcl.ac.uk.

We thank you for your time to complete all items.

Patient information sheet Version 1 (Dated 22/07/2015)

Re: Clinical Study Short Title of Study:

Stratified medicine and technological approaches to managing chronic orofacial pain patients:

Pilot study for 500 patients

NRES Committee London - Dulwich REC Ref: 15/LO/1108

Invitation to join study

1. You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 give you more detailed information about the conduct of the study.

2. Please take time to read the following information carefully. Talk to others about the study if you wish and the following organization could give you independent advice:

King's College Hospital Foundation Trust Patient Advice and Liaison Service

Telephone 0203 299 3625 or 0203 299 3601 Email: pals@kch.nhs.uk

Post to: Patient Advice and Liaison Service King's College Hospital, London, SE5 9RS

PART 1

3. What is the purpose of the study?

As you have already been provided with a diagnosis for your orofacial pain condition, we would like to assess the sensitivity of our questionnaires by asking you to complete online questionnaires via our secure dedicated website (www.chronicorofacialpain.org.uk). The answers that you provide will result in an automated formulation of a diagnosis. A computer program will then compare your answers with the diagnosis provided to you by the clinician at the specialist orofacial pain services. We will then amend the questions depending on the sensitivity results so that these questionnaires can then be.

Once the questions have been corrected and we achieve a 90% sensitivity of the system, the principle objective of this study will then be to ultimately use these questionnaires on a larger cohort of patients (up to 3,000 patients over 5 years).

With your consent, we would also like to assess specific demographic and psychological traits, together with biological pain markers within any blood/saliva samples that you may have provided us in the past. If you do agree, these samples would be assessed via the BioResource. Outcomes of such assessments may facilitate us with prescribing the correct management methods that will help reduce the overall experience of symptoms and improve quality of life.

4. Why have I been chosen?

You have been chosen to participate in this study because you have already been seen at our specialist orofacial pain clinic, and diagnosed with a chronic pain condition that affects the oral and/or facial region(s).

5. Do I have to take part?

Taking part is completely optional.

Similarly, you will also have the option of whether or not you would like to participate in the BioResource.

You will have the right to withdraw from the study and NIHR BioResource at any point. This will not affect the standard of care that you receive.

6a. What will happen to me if I take part?

This study will assess the efficiency of using online methods of collecting data for improving patient diagnostics and management. You will be provided with information and details about a link to our dedicated website (www.orofacialpain.org.uk) for chronic orofacial pain patients. Upon entering the patient area within this website and registering your details (providing just your name, referrer details and email address), you will then be provided with a unique personal log-in code to enter the key area containing the questionnaires. You must complete these questionnaires, as your answers will allow the formulation of an automated diagnosis.

The automated diagnosis will be recorded and compared with the diagnosis that had already been provided to you at your clinical appointment with us.

We would also like to obtain blood samples from you upon your informed consent, to allow the assessment of specific pain markers through the NIHR BioResource at Guys and St. Thomas' NHS Foundation Trust and KCL. We will collect the sample at clinical appointment and at any subsequent review appointment. If you are unable or unwilling to provide blood, you may provide a saliva sample instead.

6b. Taking part in the NIHR BioResource

As well as asking you to take part in the orofacial pain study, we would also like to ask you to participate in the NIHR BioResource initiative at Guy's and St. Thomas' Hospitals. As our research develops, it is possible that we will want material from your blood (or saliva if blood cannot be obtained) sample and related data to be shared with other biomedical researchers, including those from other countries, and those working on studies other than orofacial pain.

We are therefore also asking you to agree to be part of a group of individuals who are willing to consider being involved in future research projects and are happy to be selected for these projects on the basis of genetic/biochemical results obtained from your donated sample and other information provided or obtained from your medical notes. You will form part of the NIHR BioResource at Guy's & St Thomas' NHS Foundation Trust and King's College London (GSTT/KCL), which is part of a national project supported by the Department of Health National Institute for Health Research (NIHR) involving clinicians and researchers in other centres across the UK who are establishing similar collections - collectively called the NIHR BioResource).

As a member of the NIHR BioResource, you will only be approached about additional research projects, which have been approved by an ethics committee. We would never ask you to consider joining a study that had not been properly approved. Each new study we ask you to consider being involved in would be explained to you and would come with its own information sheet and consent form. We will not approach you more than 4 times per year.

If you subsequently change your mind and no longer wish to be considered for future research you can withdraw from the NIHR BioResource at any time without affecting your involvement in the main project or any other aspect of the clinical care you receive. We will simply note in our records that you are happy to allow us to continue to work on the samples already provided but do not wish to be contacted again in the future to consider any further projects.

7. What do I have to do?

Firstly, please ensure you have an email address, as this will be required during the registration process.

You should then enter the patient area of our dedicated website for chronic orofacial pain (www.orofacialpain.org.uk), as indicated by information provided in your appointment letter. From there, you will be able to register for entry to the study.

Upon registration, you will be sent a unique ID code and password in order to enter the main area containing the questionnaires on your general demographics, pain history, psychological measures and quality of life.

At your clinical appointment and subsequent review appointments, we would also like to collect blood (or saliva) samples from you for genetic analysis via the NIHR BioResource at Guy’s and St. Thomas’ Hospitals, to see which pain markers have increased/decreased.

8. What are the approaches that are being tested?

We are assessing the sensitivity of online questionnaires in correctly diagnosing patients with chronic orofacial pain conditions. Furthermore, we are assessing the expression of specific genetic markers involved in pain perception.

We are not testing any other drug or device. Any medications or treatment methods provided to you at your clinical appointment with a specialist will be part of routine clinical care that is regularly used to treat orofacial pain.

9. What are the alternatives for diagnosis or treatment?

The questionnaires that you will complete are already used as routine standard practice. Furthermore, you have already been provided with a diagnosis for your orofacial pain condition.

10. What are the possible disadvantages and risks of taking part?

The collection of routine clinical data via online questionnaires will not pose any major risks, intrusion or burden to you. You will be using a unique ID number to enter the main system with these questionnaires, which will ensure that all data that you provide will be in anonymised format. All of the data that you provide will therefore be secure.

You may, however, feel some discomfort or pain during obtaining the blood samples but appropriately trained members of staff will try their best to keep these pain levels minimal during the procedure.

11. What are the possible benefits of taking part?

Your answers to the online questionnaires will help develop online questions that will be sensitive enough to provide accurate diagnoses of patients in the future. Once our system has been developed, we will be able to use this system to assess up to 3,000 patients over 5 years at King's College Hospital.

In addition to these benefits, your answers to the online questionnaires and blood (or saliva) samples will provide us with a large amount of data summarizing your demographics, relevant history, pain levels, functional problems and psychological profiling.

In the future, patients may be referred to the appropriate specialist within multi-disciplinary teams if urgent care is indicated by the results of these questionnaires, and help save a lot of valuable time on clinic. Consequently, you could also receive improved management of your painful condition.

The results of this study may also help hurry up referrals, thus also improving care for other patients with similar conditions. The number of consultations that you have with the consultant may also reduce due to the improved management. Furthermore, your overall level of satisfaction with your treatment could significantly improve.

We will assess your overall satisfaction with this study once you have completed the online questionnaires, and at your subsequent review appointment(s).

This project will also enable us to set standards for patient diagnosis and management, and education of both patients and clinicians.

12. What happens when the research study stops?

We aim to publish anonymised summaries of the results in medical journals. No patients will be identifiable in any publication or report emanating from the database. We will publish links to abstracts of these journal articles on our website (www.orofacialpain.org.uk). Access to the full article(s) may not be possible, however, without a subscription to the journal(s).

13. What if there is a problem? And contact details:

If you have any problems completing the questionnaires, you can contact Professor Tara Renton on: 020 3299 4255 OR Email: Tara.renton@kcl.ac.uk

If you do not have access to the internet, there will be the option of completing the questionnaires in the waiting room. You will be able to do this either by using a Tablet, or alternatively by completing hard-copies of the questionnaires.

If there is a problem with the collection of blood samples from you, we will ask whether you would be willing to provide saliva samples instead.

14. Will my taking part in the study be kept confidential?

All the information collected about you during the course of this study will be kept strictly confidential. You will be provided with a unique ID code for entering the main area containing the questionnaires, therefore all your results will be anonymised. Only the clinician(s) directly involved in your care, and the key members of the team involved in the research aspects of this study will have full access to your records. We will not publish any of your personal information to third parties.

Similarly, all blood/saliva samples collected from you will be uniquely coded for anonymisation.

15. Contact for further information:

Professor Tara Renton 0203 299 4255 OR Email: Tara.renton@kcl.ac.uk

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation,

Please continue to read the additional information in Part 2 before making any decision.

16. What if relevant new information becomes available?

We are a leading establishment in this area of research and if any new information relevant to this study becomes available, the researchers will discuss this with you. You are free to opt out of the research component of this study at any time.

17. What will happen if I don't want to carry on with the study?

You can withdraw your participation in this research at any time. This will not affect the clinical care that you receive, and you will still be able to attend further clinical appointments with us.

Information you provided through answering the questionnaires will be removed from the database by the data controller, but the overall clinical report summarizing your results will remain in your medical notes.

18. What if there is a problem?

This study is sponsored by King's College London. If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions, through contacting the Lead Investigator Professor Tara Renton on 0203 299 4255 OR Email Tara.renton@kcl.ac.uk

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. Details of how to complain can be obtained from Patient Advice and Liaison Service (PALS).

Telephone 0203 299 3625 or 0203 299 3601 Email: pals@kch.nhs.uk

19. Will my taking part in this study be kept confidential?

You will only be providing sensitive, identifiable data when you first register for entry to the area of the website containing the online questionnaires. You will then be automatically sent a unique username code and password in order to enter the area containing the online questionnaires.

All sensitive information you provided during registration will be encrypted and kept within an NHS computer, separate from your answers to the questionnaires. Hard copies of your personal data will be kept in your medical notes and a Trial Master File for this study, which will be kept in a locked filing cabinet within a secured room. Only clinicians and researchers directly involved in your care, who have had training in the 'Data Protection Act' and 'Good Clinical Practice', will have access to the databases containing answers of the questionnaires and your identifiable information.

Where publications of your direct quotations of, for example your descriptions of pain experience occur, your name will not be included in such publications. We will anonymise the statement by saying 'Patient A' etc.

All of your data collected for the NIHR BioResource will be recorded at the time of consent and sample provision as a paper record. This information will be entered on to the NIHR BioResource database on the encrypted University server. None of your information will be passed on to other researchers unless you provide your consent.

20. What will happen to any samples I give?

Any blood (or saliva) samples that you provide in this study will be coded and transferred to the NIHR BioResource at Guys and St. Thomas' Hospital NHS Foundation Trust for storage and further analysis.

21. Will any genetic tests be done?

DNA will be extracted from blood samples and stored for genotyping through the Genome-Wide Association Study (GWAS). This will allow the assessment of specific genes that are known to be involved in feeling pain.

22. What will happen to the results of the research study?

Regardless of whether or not you would like to participate with the research study, the results of the questionnaires that you complete will contribute to your clinical assessment. We will share and discuss these results with you at your consultation.

If you do agree for your results to be involved in the research study, the overall results of all participants involved this research study will be published in an anonymous format in medical journals. Participants will not be identifiable in any report or publication. Links to only the abstracts of these publications will also be published online in our website (www.orofacialpain.org.uk). Full access to these publications may only be available via subscription to the journal, or if the journal is "open access" to the public.

23. Who has reviewed this study?

This study was given a favourable ethical opinion for conduct in the NHS (or private sector) by the NRES Committee London - Dulwich (REC Ref: 15/LO/1108)

Thank you for considering to take part or taking time to read this sheet – please ask any questions if you need to.

Title of project: Re: Clinical Study

Short Title of Study:

Stratified medical and technological approaches to managing chronic orofacial pain patients.

NRES Committee London - Dulwich Ref: 15/L0/1108

PI: Professor Tara Renton

Insert your NHS number

Please insert your initials if you give your consent to the following:

Initials

1. I confirm that I have read and understand the information sheet dated 22/07/2015 (Version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

1. I confirm that I have read and understand the information sheet dated 22/07/2015 (Version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. Initials

2. I understand that contributing to this research database is completely voluntary and that I am free to withdraw my consent to storing my answers on the research database at any time, without giving any reason, without my medical care or legal rights being affected.

2. I understand that contributing to this research database is completely voluntary and that I am free to withdraw my consent to storing my answers on the research database at any time, without giving any reason, without my medical care or legal rights being affected. Initials

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by responsible individuals from the Dental Institute at King's College Hospital, or from the regulatory authorities, or from King's College London, where it is relevant to my taking part in this research.

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by responsible individuals from the Dental Institute at King's College Hospital, or from the regulatory authorities, or from King's College London, where it is relevant to my taking part in this research. Initials

4. I agree to my GP being informed of my participation in the study.

4. I agree to my GP being informed of my participation in the study. Initials

5. I understand that I will not be identifiable in any publication or report emanating from the database.

5. I understand that I will not be identifiable in any publication or report emanating from the database. Initials

6. I agree to the storage and analysis of my answers to the questionnaires for research purposes.

6. I agree to the storage and analysis of my answers to the questionnaires for research purposes. Initials

7. I agree to provide blood samples and to join the NIHR BioResource at Guy's & St Thomas' NHS Foundation Trust and happy to consider involvement in research projects by other researchers, including those looking at diseases other than orofacial pain. I understand that my contact details will not be passed to such researchers without my consent and once notified about a project there is no obligation for me to get involved. Previously collected blood samples can also be transferred to the NIHR BioResource. If blood cannot be taken for any reason, I agree to provide saliva samples instead.

7. I agree to provide blood samples and to join the NIHR BioResource at Guy's & St Thomas' NHS Foundation Trust and happy to consider involvement in research projects by other researchers, including those looking at diseases other than orofacial pain. I understand that my contact details will not be passed to such researchers without my consent and once notified about a project there is no obligation for me to get involved. Previously collected blood samples can also be transferred to the NIHR BioResource. If blood cannot be taken for any reason, I agree to provide saliva samples instead. Initials

8. I agree that DNA will be isolated from my donated tissue sample and analysed through the use of advanced laboratory techniques.

8. I agree that DNA will be isolated from my donated tissue sample and analysed through the use of advanced laboratory techniques. Initials

9. I agree to allow material from my sample and related data to be shared with other biomedical researchers, including those looking at diseases other than orofacial pain.

9. I agree to allow material from my sample and related data to be shared with other biomedical researchers, including those looking at diseases other than orofacial pain. Initials

10. I give permission for GSTT NIHR BioResource to access my medical notes and other health-related records.

10. I give permission for GSTT NIHR BioResource to access my medical notes and other health-related records. Initials

Tick this box to electronically sign this consent form

Yes, I give my provisional consent and understand that I will need to sign a full consent form at my appointment

Patient Referral to Us

Did your symptoms of pain and/or discomfort affecting the oral and/or facial region(s) start suddenly, for no apparent reason? *

Yes No Don't Know

Patient Referral to Us: Patient details

Your Details

Name E-mail address

Who has referred you? Is it your: *

General Dental Practitioner General Medical Practitioner Other (please specify):

Appendix 3

Diagnostic sheet

Clinician Date

TMD Pain	M25.58		*Nervus intermedius neuralgia*	G51.1
Pain in joint TMJ (dysfunctional)	M25.58a		*Disorders of Trigeminal nerve, unspecified*	G50.9
• Disc displacement with reduction • Disc displacement without reduction	M25.58aa M25.58ab		*Unspecified disturbances of smell and taste*	R43.8
Pain in joint TMJ (Myo-facial)	M25.58b		*Injury of Facial nerve*	S04.5
Pain in joint TMJ (Arthritic)	M25.58c		*Disorders of multiple cranial nerves*	G52.7
Pain in joint TMJ (Traumatic)	M25.58d		*Other symptoms and signs involving the nervous / musculoskeletal systems*	R29.8
NEUROPATHIC			**Neurological Related Causes of Pain**	
Injury of Trigeminal nerve (Traumatic)	S04.3		Central post stroke pain (169.4)	G93.8
• Surgical trauma (Wisdom tooth surgery)	S04.3a		Disorders of Central nervous system (Unspecified)	G96.9
• Surgical trauma (Implant placement)	S04.3b		*Neuralgia and neuritis, unspecified, multiple sites*	M79.20
• Chemical Trauma (LA injection)	S04.3c			
• Chemical Trauma (Endodontics)	S04.3d		***NEUROVASCULAR***	R51.0
Diabetes	E08.42		**Primary Headaches (Migraine)**	
Radiotherapy	G62.8		Migraine without aura (Common Migraine)	G43.0
Chemotherapy	Z51.1		Migraine with aura (Classical Migraine)	G43.1
Neoplasia	C01-C10.9		Complicated Migraine	G43.3
Infections (Soft tissue)	K12.2		Other Migraine	G43.8
Fractures of Skull & Facial bones	S02.00		Migraine unspecified	G43.9
Fracture of alveolus (Maxilla)	S02.42		Status migrainous chronic migraine	G43.2
Fracture of alveolus (Mandible)	S04.67			
Sickle cell	D57.00		**Daily Headaches**	
Facial Pain associated MS	G35.0		New daily persistent headache	G44.8
Malignant neoplasm of mouth	C06.9		Tension headache	G44.1
Chronic sinusitis, antrum	M86.9		Medication overuse headaches	G44.4
Infection bone/(Osteomyelitis)	K10.2		Other specified headache syndromes	G44.8
Others			Cervicogenic headaches	G44.8
Burning mouth glossodynia	K14.6		Headache attributed to TMPD	
• Burning mouth Primary	K14.6a		Headache attributed to spontaneous intracranial.	R51.0 + 195.8
• Burning mouth Secondary	K14.6b		Hypotension no code for IH	
Primary neuropathies			Vascular headache, not elsewhere classified	G44.1

Trigeminal Neuralgia classic	G50.0		Chronic post-traumatic headaches	G44.3
Trigeminal neuralgia (non-classical Atypical)	G50.0.c4		***DENTAL***	
Occipital neuralgia	G52.8		Dentinal Hypersensitivity	K03.89
Glossopharyngeal neuralgia	G52.1		Dental Caries	K02.9
Others disorders of Trigeminal neuralgia	G50.8		Dental Caries (Radicular Cyst)	K02.9b
Trigeminal Autonomic Cephalgia (TAC)			Pericoronitis	K05.3
Cluster Headache syndrome	G44.0		Impacted tooth	K01.1
Other trigeminal autonomic Cephalgias	G44.8		Impacted tooth (With Cyst)	K01.1a
• SUNCT	G44.05		Retained Dental root	K08.3
• SUNA			Dry Socket (Alveolar osteitis)	K10.3
• Hemicrania	G44.51		Periapical Abscess	K04.7
• Paroxysmal Hemicrania	G44.03		Osteochemonecrosis (BRONJ)	M87.180
Giant cell arteritis	M31.6		Osteoradionecrosis	K10.2
			SITE CODES	
IDIOPATHIC			Right	R
Persistent Idiopathic Facial Pain (PIFA)	G50.1		Left	L
• Intraoral	G50.1a		Bilateral	Bi
• Extra-oral	G50.1b		Ophthalmic branch nerve	V1
Persistent Dento-alveolar (PDAP)			Maxillary branch nerve	V2
Idiopathic Trigeminal Neuropathy	G50.8a		Mandibular branch Nerve	V3
PSYCHIATRIC			• Lingual • IAN	V3l V3i
Other Single mood (affective) Disorder	F38.0		TMJ	Z65.2
Depressive Disorders	F32.9		Cervical Muscles	Z60.2
Generalised Anxiety Disorder	F41.1		Trigeminal Nerve (V)	Z03.5
Mixed anxiety and depressive disorder	F41.2		*Lower Cranial Nerves (NEC)*	Z04.7
Post-traumatic stress disorder	F43.1		*Cranial Nerves (NEC)*	Z04.9
Adjustment Disorder	F43.2		*Meninges surrounding Optic nerve*	Z05.7
Cancer Phobia (Hypochondriacal disorder)	F45.2		*Spinal nerve C-spine, C2, C3*	Z07.1

Appendix 4

4.1. Questionnaire Pack

If you are experiencing pain, please complete all questionnaires in the pack

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about □

I have slight problems in walking about □

I have moderate problems in walking about □

I have severe problems in walking about □

I am unable to walk about □

SELF-CARE

I have no problems washing or dressing myself □

I have slight problems washing or dressing myself □

I have moderate problems washing or dressing myself □

I have severe problems washing or dressing myself □

I am unable to wash or dress myself □

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities □

I have slight problems doing my usual activities □

I have moderate problems doing my usual activities □

I have severe problems doing my usual activities □

I am unable to do my usual activities □

PAIN / DISCOMFORT

I have no pain or discomfort □

I have slight pain or discomfort □

I have moderate pain or discomfort □

I have severe pain or discomfort □

I have extreme pain or discomfort □

ANXIETY / DEPRESSION

I am not anxious or depressed □

I am slightly anxious or depressed □

I am moderately anxious or depressed □

I am severely anxious or depressed □

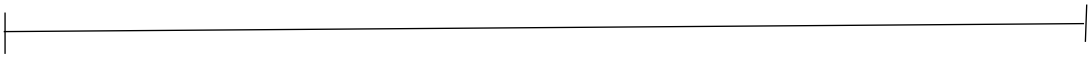
I am extremely anxious or depressed □

- We would like to know how good or bad your health is

TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale and in the box below

Your Health Today



0 50 100

The worst health you can imagine

The best health you can imagine

GAD

Over the last 2 weeks, how often have you been bothered by the following problems?

Not at all sure	Several days	Over half the days	Nearly every day
0	1	2	3

1. Feeling nervous, anxious, or on edge □
2. Not being able to stop or control worrying □
3. Worrying too much about different things □
4. Trouble relaxing □
5. Being so restless that it's hard to sit still □
6. Becoming easily annoyed or irritable □
7. Feeling afraid as if something awful might happen □

Add the score for each column + + +

Total GAD Score (add your column scores) =

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. Arch Inern Med. 2006;166:1092-1097.

Patient Health Questionnaire (PHQ-9)

PHQ-9 Depression Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use the following scale to indicate your answer)

Not at all	Several days	More than half the days	Nearly every day
0	1	2	3

1. Little interest or pleasure in doing things

2. Feeling down, depressed, or hopeless

3. Trouble falling or staying asleep, or sleeping too much

4. Feeling tired or having little energy

5. Poor appetite or overeating

6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down

7. Trouble concentrating on things, such as reading the newspaper or watching television

8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving .around a lot more than usual

9. Thoughts that you would be better off dead or of hurting yourself in some way

Column totals ___ + ___ + ____ + ___ =

Total Score _____

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people

Not difficult at all----------

Somewhat difficult----------

Very Difficult----------

Extremely difficult----------

Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues. For research information, contact Dr. Spitzer at rls8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. C

Multidimensional scale of perceived social support

Multidimensional Scale of Perceived Social Support

Instructions: We are interested in how you feel about the following statements. Read each statement carefully. Indicate how you feel about each statement.

Circle the “1” if you Very Strongly Disagree

Circle the “2” if you Strongly Disagree

Circle the “3” if you Mildly Disagree

Circle the “4” if you are Neutral

Circle the “5” if you Mildly Agree

Circle the “6” if you Strongly Agree

Circle the “7” if you Very Strongly Agree

1. There is a special person who is around when I am in need. 1 2 3 4 5 6 7

2. There is a special person with whom I can share joys and sorrows. 1 2 3 4 5 6 7

3. My family really tries to help me. 1 2 3 4 5 6 7

4. I get the emotional help & support I need from my family. 1 2 3 4 5 6 7

5. I have a special person who is a real source of comfort to me. 1 2 3 4 5 6 7

6. My friends really try to help me. 1 2 3 4 5 6 7

7. I can count on my friends when things go wrong. 1 2 3 4 5 6 7

8. I can talk about my problems with my family. 1 2 3 4 5 6 7

9. I have friends with whom I can share my joys and sorrows. 1 2 3 4 5 6 7

10. There is a special person in my life who cares about my feelings. 1 2 3 4 5 6 7

11. My family is willing to help me make decisions. 1 2 3 4 5 6 7

12. I can talk about my problems with my friends. 1 2 3 4 5 6 7

Scale Reference:

Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support.

Journal of Personality Assessment 1988; 52:30-41.

Scoring Information:

To calculate mean scores:

Significant Other Subscale: Sum across items 1, 2, 5, & 10, then divide by 4.

Family Subscale: Sum across items 3, 4, 8, & 11, then divide by 4.

Friends Subscale: Sum across items 6, 7, 9, & 12, then divide by 4.

Total Scale: Sum across all 12 items, then divide by 12.

More information at:

http://gzimet.wix.com/mspss

Other MSPSS Scoring Options:

There are no established population norms on the MSPSS. Also, norms would likely vary on the basis of

culture and nationality, as well as age and gender. I have typically looked at how social support differs

between groups (e.g., married compared to unmarried individuals) or is associated with other measures (e.g.,

depression or anxiety). With these approaches you can use the mean scale scores.

If you want to divide your respondents into groups on the basis of MSPSS scores there are at least two ways

you can approach this process:

1. You can divide your respondents into 3 equal groups on the basis of their scores (trichotomize) and

designate the lowest group as low perceived support, the middle group as medium support, and the high

group as high support. This approach ensures that you have about the same number of respondents in each

group. But, if the distribution of scores is skewed, your low support group, for example, may include

respondents who report moderate or even relatively high levels of support.

2. Alternatively, you can use the scale response descriptors as a guide. In this approach any mean scale score

ranging from 1 to 2.9 could be considered low support; a score of 3 to 5 could be considered moderate

support; a score from 5.1 to 7 could be considered high support. This approach would seem to have more

ORAL HEALTH IMPACT PROFILE

HOW OFTEN have you had the problem during the last year?

(Circle your answer)

1. Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON'T KNOW

2. Have you felt that your sense of taste has worsened because of problems with your teeth, mouth or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON'T KNOW

3. Have you had painful aching in your mouth?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON'T KNOW

4. Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth

or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON’T KNOW

5. Have you been self-conscious because of your teeth, mouth or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON’T KNOW

6. Have you felt tense because of problems with your teeth, mouth or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON’T KNOW

7. Has your diet been unsatisfactory because of problems with your teeth, mouth or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON’T KNOW

8. Have you had to interrupt meals because of problems with your teeth, mouth or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON’T KNOW

9. Have you found it difficult to relax because of problems with your teeth, mouth or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON’T KNOW

10. Have you been a bit embarrassed because of problems with your teeth, mouth or dentures?

VERY OFTEN

FAIRLY OFTEN

OCCASIONALLY

HARDLY EVER

NEVER

DON’T KNOW

ORAL HEALTH IMPACT PROFILE

1

Oral Health Impact Profile (OHIP-14/Slade 1997) Oral Health-Related Quality of Life Measure

HOW OFTEN have you had the problem during the last year?

(circle your answer)

11. Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures?

VERY

OFTEN

FAIRLY

OFTEN

OCCASIONALLY

HARDLY

EVER

NEVER DON’T

KNOW

12. Have you had difficulty doing your usual jobs because of problems with your teeth, mouth or dentures?

VERY

OFTEN

FAIRLY

OFTEN

OCCASIONALLY

HARDLY

EVER

NEVER DON’T

KNOW

13. Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?

VERY

OFTEN

FAIRLY

OFTEN

OCCASIONALLY

HARDLY

EVER

NEVER DON’T

KNOW

14. Have you been totally unable to function because of problems with your teeth, mouth or dentures?

VERY

OFTEN

FAIRLY

OFTEN

OCCASIONALLY

HARDLY

EVER

NEVER DON’T

KNOW

PCL (Brief Version)

Patient name: ---------- Date: ----------

Instructions: Below is a list of problems and complaints which people may experience after a nerve injury. Please read each one carefully. Then circle one of the numbers to the right to indicate how much you have been bothered by the problem

Bothered by	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Avoiding activities or situations because they remind you of the experience?	1	2	3	4	5
2. Loss of interest in activities that you used to enjoy?	1	2	3	4	5
3. Feeling distant or cut off from other people?	1	2	3	4	5
4. Feeling emotionally numb or being unable to have loving feelings for those close to you?	1	2	3	4	5
5. Trouble falling or staying asleep?	1	2	3	4	5
6. Being jumpy or easily startled?	1	2	3	4	5

The Pain Catastrophizing Scale (PCS)

Instructions: We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are 13 statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 1 2 3 4

Not at all, To a slight degree, To a moderate degree, To a great degree, All the time

When I'm in pain . . .

1. I worry all the time about whether the pain will end . . . . . _____

2. I feel I can't go on . . . . . _____

3. It's terrible and I think it's never going to get any better . . . . . _____

4. It's awful and I feel that it overwhelms me . . . . . _____

5. I feel I can't stand it anymore . . . . . _____

6. I become afraid that the pain will get worse . . . . . _____

7. I keep thinking of other painful events . . . . . _____

8. I anxiously want the pain to go away . . . . . _____

9. I can't seem to keep it out of my mind . . . . . _____

10. I keep thinking about how much it hurts . . . . . _____

11. I keep thinking about how badly I want the pain to stop . . . . . _____

12. There's nothing I can do to reduce the intensity of the pain . . . . . _____

13. I wonder whether something serious may happen . . . . . _____

Note. Reprinted from "The Pain Catastrophizing Scale: development and validation" by M. J. L. Sullivan, S. Bishop, and J. Pivik, (1995), Psychological Assessment, 7 , pp. 524–532. Copyright 1995 by Michael J. L. Sullivan. Reprinted with permission.

CPAQ-8

Directions: Below you will find a list of statements. Please rate the truth of each statement as it applies to you. Use the following rating scale to make your choices. For instance, if you believe a statement is 'Always True,' you would write a 6 in the blank next to that statement.

Never True	Very rarely true	Seldom true	Sometimes true	Often true	Almost always true	Always true
0	1	2	3	4	5	6

1. I am getting on with the business of living no matter what my level of pain is.	0123456
2. Keeping my pain level under control takes first priority whenever I'm doing something.	0123456
3. Although things have changed, I am living a normal life despite my chronic pain.	0123456
4. Before I can make any serious plans, I have to get some control over my pain.	0123456
5. I lead a full life even though I have chronic pain.	0123456
6. When my pain increases, I can still take care of my responsibilities.	0123456
7. I avoid putting myself in situations where my pain might increase.	0123456
8. My worries and fears about what pain will do to me are true.	0123456

Note: Pain willingness scale items 2, 4, 7 and 8 (reverse scored)

Activity engagement scale items 1, 3, 5 and 6

Total = activity engagement + pain willingness

Short-form McGill Pain Questionnaire 2 (SF-MPQ-2)

Patient ID:

Date

For this questionnaire, I will provide you a list of words that describe some of the different qualities of pain and related symptoms. Please rate the intensity of each of the pain and related symptoms you felt during the past week on 0 to 10 scale, with 0 being no pain and 10 being the worst pain you can imagine. Use 0 if the word does not describe your pain or related symptoms. Limit yourself to a description of the pain related to your surgery or pelvic pain.

1. Throbbing pain none 1 2 3 4 5 6 7 8 9 10 worst possible
2. Shooting pain none 1 2 3 4 5 6 7 8 9 10 worst possible
3. Stabbing pain none 1 2 3 4 5 6 7 8 9 10 worst possible
4. Sharp pain none 1 2 3 4 5 6 7 8 9 10 worst possible
5. Cramping pain none 1 2 3 4 5 6 7 8 9 10 worst possible
6. Gnawing pain none 1 2 3 4 5 6 7 8 9 10 worst possible
7. Hot-burning pain none 1 2 3 4 5 6 7 8 9 10 worst possible
8. Aching pain none 1 2 3 4 5 6 7 8 9 10 worst possible
9. Heavy pain none 1 2 3 4 5 6 7 8 9 10 worst possible
10. Tender none 1 2 3 4 5 6 7 8 9 10 worst possible
11. Splitting pain none 1 2 3 4 5 6 7 8 9 10 worst possible
12. Tiring-exhausting

    none1 2 3 4 5 6 7 8 9 10 worst possible
13. Sickening none 1 2 3 4 5 6 7 8 9 10 worst possible
14. Fearful none 1 2 3 4 5 6 7 8 9 10 worst possible
15. Punishing-cruel

    None 1 2 3 4 5 6 7 8 9 10worst possible
16. Electric-shock pain

    None 1 2 3 4 5 6 7 8 9 10 worst possible
17. Cold-freezing pain

    None 1 2 3 4 5 6 7 8 9 10 worst possible
18. Piercing none 1 2 3 4 5 6 7 8 9 10 worst possible

19. Pain caused by light touch

None 1 2 3 4 5 6 7 8 9 10 worst possible

20. Itching none 1 2 3 4 5 6 7 8 9 10 worst possible

21. Tingling or ‘pins and needles’

None 1 2 3 4 5 6 7 8 9 10 worst possible

22. Numbness none1 2 3 4 5 6 7 8 9 10 worst possible

23. Present Pain Intensity (PPI) – Numerical Pain Rating Scale. On a scale from zero to ten, zero indicating no pain and ten indicating worst pain imaginable, rate your pain:

None 1 2 3 4 5 6 7 8 9 10 worst possible

24. Evaluative overall intensity of total pain experience. Please check (√) the word that describes the pain in your pelvic area only.

D No pain D Mild D Discomforting D Distressing D Horrible D Excruciating

painDETECT

How would you assess your pain **now**, at this moment?

None 0 1 2 3 4 5 6 7 8 9 10 max.

How strong was the **strongest** pain during the past 4 weeks?

None 0 1 2 3 4 5 6 7 8 9 10 max.

How strong was the pain during the past 4 weeks **on average**?

None 0 1 2 3 4 5 6 7 8 9 10 max.

Please mark your

main area of pain

Does your pain radiate to other

regions of your body? Yes

no

If yes, please draw the direction

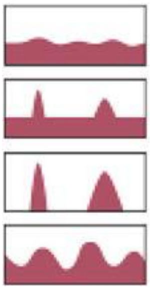
in

Which the pain

radiates.

Mark the picture that best describes the course of your

Mark the picture that best describes the course of your pain:



1. Persistent pain with slight fluctuations

2. Persistent pain with pain attacks

3. Pain attacks without pain between them

4. Pain attacks with pain between them

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?

Never hardly noticed slightly moderately strongly very strongly

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

Never hardly noticed slightly moderately strongly very strongly

Is light touching (clothing, a blanket) in this area painful?

Never hardly noticed slightly moderately strongly very strongly

Do you have sudden pain attacks in the area of your pain, like electric shocks?

Never hardly noticed slightly moderately strongly very strongly

Is cold or heat (bath water) in this area occasionally painful?

Never hardly noticed slightly moderately strongly very strongly

Do you suffer from a sensation of numbness in the areas that you marked?

Never hardly noticed slightly moderately strongly very strongly

Does slight pressure in this area, e.g., with a finger, trigger pain?

Never hardly noticed slightly moderately strongly very strongly

(To be filled out by the physician)

Never hardly noticed slightly moderately strongly very strongly

□x 0 = 0 □ x 1 = □ x 2 = □x 3 = □x 4 = □x 5 =

Total score out of 35

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006) ©2005 Pfizer Pharma GmbH

□□
□□□□□□□□□□□□□□□□□□□□□□□

SCORING OF PAIN QUESTIONNAIRE

Date: _____ Patient: Last name: _____ First name: _____

‘

Please transfer the total score from the pain questionnaire:

Total score

Please add up the following numbers, depending on the marked pain behaviour pattern and the pain radiation. Then total up the final score:

0 Persistent pain with slight fluctuations

- 1 Persistent pain with pain attacks

if marked, or

+ 1 Pain attacks without pain between them

if marked, or

+ 1 Pain attacks with pain between them

if marked

+ 2 Radiating pains?

if yes

Final score

Screening Result

Final score

Nociceptive unclear neuropathic

A neuropathic pain component is unlikely (< 15%)

Result is ambiguous,

However a neuropathic pain component can be present

A neuropathic pain component is likely (> 90%)

This sheet does not replace medical diagnostics.

It is used for screening the presence of a neuropathic pain component.

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006)

PAIN SELF EFFICACY QUESTIONNAIRE (PSEQ)

M.K.Nicholas (1989)

NAME: _____ DATE: _____

Please rate how confident you are that you can do the following things at present, despite the pain. To indicate your answer circle one of the numbers on the scale under each item, where 0 = not at all confident and 6 = completely confident.

For example:

Not at 0-------1--------2--------3-------4---------5---------6 Completely

Confident confident

Remember, this questionnaire is not asking whether of not you have been doing these things, but rather how confident you are that you can do them at present, despite the pain.

1. I can enjoy things, despite the pain.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely

Confident confident

2. I can do most of the household chores (e.g. tidying-up, washing dishes, etc.), despite the pain.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely

Confident confident

3. I can socialise with my friends or family members as often as I used to do, despite the pain.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely

Confident confident

4. I can cope with my pain in most situations.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely

Confident confident

Turn over

5. I can do some form of work, despite the pain. ("work" includes housework, paid and unpaid work).

Not at all 0-------1--------2--------3-------4---------5---------6 Completely

Confident confident

6. I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite pain.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely

Confident confident

7. I can cope with my pain without medication.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely Confident confident

8. I can still accomplish most of my goals in life, despite the pain.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely Confident confident

9. I can live a normal lifestyle, despite the pain.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely Confident confident

10. I can gradually become more active, despite the pain.

Not at all 0-------1--------2--------3-------4---------5---------6 Completely Confident confident

Source: Nicholas M.K. Self-efficacy and chronic pain. Paper presented at the annual conference of the British

Psychological Society. St. Andrews, 1989.

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Appendix 4.2

4.2. Questionnaire cut off

General Anxiety Disorder; GAD 5-9 score is mild anxiety, GAD 10-14 score is moderate anxiety and GAD 15+ score indicates severe anxiety

Patient Health Questionnaire; PHQ 5-9 score is mild depression, PHQ 10-14 score is moderate depression, PHQ 15-19 is moderately severe depression, PHQ 20-27 score indicates severe depression

Patient Catastrophizing Scale PCS score is 0-52, high score indicates high catastrophizing, score above 38 is clinically relevant. Cut off pre-treatment score is at 20 (Scott et al., 2014)

Chronic pain acceptance questionnaire CPAQ score 0-60, add all scores, higher score means high level of acceptance

Pain Self Efficacy Questionnaire PSEQ score 0-60, add all the score, higher score means stronger self-efficacy believes. Score <20 means patient is focused on pain. If > 40 means the patient is likely to improve due to their positive beliefs (Nicholas, 2007).

Oral Health Impact Profile OHIP-14 mean score indicate how much the quality of life of an individual is affected by pain

Short-form McGill pain Questionnaire-2 SF-MPQ-2, consists of 22 different descriptors of pain and each item is rated based on a 0-10 scale with 0 equal to no pain and 10 equal to the worst pain ever during the past week. The total score is calculated by summing 22 individual scores. SF-MPQ-2 comprises of 4 parts including Continuous (throbbing pain, cramping pain, gnawing pain, aching pain, heavy pain, tender), Intermittent (shooting pain, stabbing pain, sharp pain, splitting pain, electric-shock pain, piercing), Neuropathic (hot-burning pain, cold-freezing pain, pain caused by light touch, itching, tingling or “pins and needles”, numbness), and Affective (tiring-exhausting, sickening, fearful, punishing-cruel) subscales (Dworkin et al., 2015).

Appendix 5

Patient outcome questionnaire

Please indicate, by circling the number or word, which of the following reflects your progress since being referred to this service

1st visit

Do you understand your diagnosis? Please circle as appropriate, where **1 = Not at all, 10 = very well**

1 2 3 4 5 6 7 8 9 10

Comment if you wish:

.....
.....

How would you rate your satisfaction with your consultation visit? 1 = Not at all; 10 = Extremely

1 2 3 4 5 6 7 8 9 10

If you feel that the consultation was not satisfactory from your point of view please explain why?

.....
.....

Please rate your pain/discomfort score:

On average (where 10 = the worst pain imaginable)

1 2 3 4 5 6 7 8 9 10

Worst Pain/discomfort

1 2 3 4 5 6 7 8 9 10

Lowest level of Pain/discomfort

1 2 3 4 5 6 7 8 9 10

Are you happy with the advice given to you today on how your complaint should be managed?

Please circle as appropriate; 1 = Not at all happy; 10 = Extremely happy

1 2 3 4 5 6 7 8 9 10

If you are not happy with today's visit how do you think this service could be improved?

.....

Clinician's notes **Patients do NOT complete**

Diagnosis 1…….

Diagnosis 2…….

Diagnosis 3…….

Investigations

- Radiographic
    - Pan-oral
    - LCPA
    - CBCT
- Haematological
- MRI

Treatments

- Consultation only
- Psychiatric apt
- ENT surgeon
- Neuro-psychologist
- Neurologist
- Neurosurgeon
- Clinical Psychologist
    - CBT
    - ACT
- Medication
    - NSAIDs
    - TCAs
    - Anti-epileptics
    - SNRIs
    - Other
- Bite-raising appliance
- other

Hospital number / sticker *Date ../. ./....* *Main complaint*

……..

Date of review appointment:

Visit number:

Were you provided with treatment at your last visit **Yes/No**

Has your condition improved since your last consultation / treatment?

Much worse no change Much better

-5 -4 -3 -2 -1 0 1 2 3 4 5

Please rate your pain/discomfort score since the last visit:

On average (where 10 = the most painful)

0 1 2 3 4 5 6 7 8 9 10

Worst Pain/discomfort

0 1 2 3 4 5 6 7 8 9 10

Lowest level of Pain/discomfort

0 1 2 3 4 5 6 7 8 9 10

Do you have more pain free days than you used to? Yes No

Are you coping better with your condition since your last visit?

Not coping coping much better

0 1 2 3 4 5 6 7 8 9 10

Please rate your quality of sleep since the last visit: 1 = Not very good; 10 = Extremely good

1 2 3 4 5 6 7 8 9 10

Apart from the medications that have been prescribed for you by your doctors, how many days per week do you use additional pain killers:

0 1 2 3 4 5 6 7

Have you been compliant with the medication or exercises or splint prescribed for you: Yes No N/A

Are you suffering from side effects from your medical or surgical treatment?

Yes No

If YES

Have these side effects prevented you from continuing your treatment?

Yes No

How would you rate your satisfaction with your consultation visit:? 0 = Not at all; 10 = Extremely satisfied

0 1 2 3 4 5 6 7 8 9 10

If you feel that the consultation was not satisfactory from your point of view please explain why?

.....
.....

How can we improve our service?

.....
.....

Clinician's notes **Patients do NOT complete**

Review appointment number:

Diagnosis 1…….

Diagnosis 2…….

Diagnosis 3…….

Investigations

- Radiographic
    - Pan-oral
    - LCPA
    - CBCT
- Haematological
- MRI

Treatments

- Consultation only
- Psychiatric apt
- ENT surgeon
- Neuro-psychologist
- Neurosurgeon
- Neurologist
- Clinical Psychologist
    - CBT
    - ACT
- Medication
    - NSAIDs
    - TCAs
    - Anti-epileptics
    - SNRIs
    - Other
- Bite-raising appliance
- other