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ORIGINAL ARTICLE

Persistent orofacial muscle pain

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The pathophysiology of persistent orofacial myalgia has been the centre of much controversy. In this article we suggest a novel descriptive term; 'persistent orofacial muscle pain' (POMP) and review current evidence that supports the hypothesis that the induction of POMP involves the interplay between a peripheral nociceptive source in muscle, a faulty central nervous system component and decreased coping ability. In this context it is widely accepted that a complex interaction of variable intrinsic and extrinsic factors act to induce POMP and dysfunction.

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Introduction

This article summarizes the major conclusions of the subcommittee on the pathophysiology of chronic regional myalgia at the fifth World Workshop on Oral Medicine held in London in September 2010.

The initial aim of the subcommittee was to publish a systematic review on the pathophysiology of regional muscle pain, commonly termed 'myofascial pain'. The methodology employed included online searches (PUBMED, Cochrane Database) of the combinations of the following terms 'temporomandibular', 'facial', 'craniofacial', 'craniomandibular', 'masticatory' with 'myalgia', 'myofascial pain' with 'aetiology', or 'pathophysiology'. A search was also performed for 'temporomandibular disorders (TMD)' and 'aetiology' or 'pathophysiology'.

It rapidly became clear that the conflicting terminology in the literature (e.g. temporomandibular dysfunction, craniomandibular dysfunction) would make this an impossible task. Additionally, many studies continue to group muscle pain and painful temporomandibular joint (TMJ) disorders together under the term TMD although these entities are pathophysiologically and clinically distinct. In part, this may be due to the large number of patients who present with comorbid muscle and TMJ pain, see (Lobbezoo *et al*, 2004). Although this may suggest a causal association or a common pathophysiology between the two there is no evidence to support this claim.

The present article therefore represents an expanded expert literature review with the committee members attempting to be as impartial, unbiased and objective as possible.

Definition

Chronic myalgia (masticatory myofascial pain) is one of the TMD (de Leeuw, 2008; Dworkin and LeResche, 1992). Unfortunately, the International Headache Society refers to chronic myalgia only as a possible initiating factor in tension-type headache (Olesen *et al*, 2004). Orofacial pain clinicians and researchers have therefore tended to use two widely accepted systems that clearly subclassify TMD into TMJ and masticatory muscle disorders; the Research Diagnostic Criteria for TMD (RDC TMD) and the definitions of the American Academy of Orofacial Pain (AAOP) (Dworkin and LeResche, 1992; de Leeuw, 2008). The RDC TMD system has recently been succesfully tested and validated (Look *et al*, 2010; Ohrbach *et al*, 2010; Schiffman *et al*,

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2010 a,b; Truelove *et al*, 2010) and has been translated into various languages so that it has wide universal acceptance. In addition to the physical diagnosis (Axis I) the RDC TMD system assesses psychological, behavioural and psychosocial factors (Axis II). The RDC TMD is currently under revision and a new set of criteria termed Diagnostic Criteria for TMD (DC TMD) should appear in the literature soon. The aims are to formulate DC TMD that are both more comprehensive and clinically useful (Anderson *et al*, 2010).

Although there is wide acceptance of (masticatory) myofascial pain as a diagnosis the working committee expressed concerns that the term may be inaccurate. Cases display important involvement of more than 'masticatory' muscles (suboccipital, neck) that account for part of the clinical presentation. The use of 'myofascial' implies unequivocal evidence that the pain arises from muscle and fascia; a contentious claim in view of current evidence. Moreover, the recurring nature of the condition is lacking in current terminologies and the temporal description 'persistent' was considered an adequate term. Thus, a novel and purely descriptive terminology is suggested: 'persistent orofacial muscle pain' (POMP).

Persistent orofacial muscle pain, is primarily characterized by unilateral pain in the temporomandibular region. Pain may be elicited, or exarcebated, by oral function and palpation of regional muscles (masticatory/pericranial, cervical); tender areas or trigger points (TrP). Muscle TrP are painful on palpation and can refer pain. These are believed to be distinct from muscle tenderness, which reflects generalized pain on palpation and sensitivity over the affected muscle. To accurately discern cases from non-cases or other orofacial pain patients, it is essential to develop a reliable technique whereby even and consistent muscle pressure is applied (Dworkin *et al*, 1990; Wolfe *et al*, 1990; Benoliel *et al*, 2008). The interincisal mouth opening may deviate to the affected side and is often limited (< 40 mm interincisal). Normal function such as chewing, talking or yawning may exarcebate pain (see Table 1). The clinical features of POMP have been extensively reviewed (Benoliel and Sharav, 2008; de Leeuw, 2008).

Epidemiology of POMP

Temporomandibular disorders are recognized as the most common persistent orofacial pain condition with no significant differences found between racial groups (Dworkin *et al*, 1990; Yap *et al*, 2003). However, not all epidemiological studies have used the same classification, or differentiated between muscle and joint disorders (LeResche *et al*, 1991). Indeed, inclusion criteria employed in studies prior to modern classifications encompassed a number of disorders into one entity. This questions the current validity of much of the epidemiological research performed prior to introduction of standardized criteria and diagnoses (Dworkin and LeResche, 1992; de Leeuw, 2008).

Signs and symptoms of TMD have been found in all age groups, peaking in 20–40 year olds (Tallents *et al*, 1991; Levitt and McKinney, 1994; List *et al*, 1999), but

Table 1 Diagnostic criteria for masticatory muscle myofascial pain

Myofascial pain (AAOP)	*Myofascial pain without/with* limited opening (RDC-TMD)* *Axis I: Physical findings*
Regional dull, aching pain	Complaint of pain of muscle origin
Aggravated by mandibular function	In jaw, temples, face, preauricular or auricular at rest or during function
Hyperirritable sites or trigger points	Pain associated with localized areas of tenderness to palpation in muscle
Frequently found within a taut band of muscle tissue or fascia	Pain on palpation in ≥3 sites of the following sites and at least one of which is ipsilateral to the pain complaint (right/left muscles count for separate sites)
Provocation of these trigger points alters the pain complaint and reveals a pattern of referral	R/L temporalis: posterior, middle, anterior, tendon (eight sites)
> 50% reduction of pain is inducible by muscle stretch preceded by trigger point treatment with	R/L masseter: origin, body, insertion (six sites)
Vapocoolant spray, or	R/L Posterior mandibular region (2 sites)
Local anaesthetic injection	R/L submandibular region (2 sites)
Signs and symptoms that may accompany pain	R/L lateral pterygoid region (2 sites)
Sensation of muscle stiffness	Myofascial pain as above accompanied by
Sensation of acute malocclusion, not clinically verified	Stiffness of muscles
Ear symptoms, tinnitus, vertigo, toothache, tension-type headache	*Pain free un-assisted mandibular opening of < 40 mm
Decreased mouth opening; passive stretching increases opening by > 4 mm	*With assistance an increase of ≥5 mm in mandibular opening
Hyperalgesia in the region of referred pain	
No psychosocial assessment required	**Axis II: Psychosocial comorbidity**[a]
	Pain intensity and pain-related disability
	Graded chronic pain scale
	Jaw disability checklist
	Depression and somatization
	Symptom checklist for depression and somatization (SCL-90)

Adapted from de Leeuw (2008) and Dworkin and LeResche (1992).
[a]Other validated measures may be used.
AAOP, American Academy of Orofacial Pain; RDC-TMD, Research Diagnostic Criteria for Temporomandibular Disorders.
*Features associated with RDCTMD classification accompanied by (with) limitation of mouth opening.

are usually milder in children (Thilander *et al*, 2002). TMD may also occur in edentulous patients (Dervis, 2004). In a longitudinal study of elderly patients, signs and symptoms of TMD tended to decrease over the follow-up period (Osterberg *et al*, 1992). These data suggest that TMD are not progressive and most symptoms resolve with increasing age. Although signs or symptoms of TMD are extremely common only 3–11% is assessed as needing treatment (Solberg *et al*, 1979; Schiffman *et al*, 1990; Magnusson *et al*, 2000).

Pathophysiology of POMP

The clinical presentation and symptoms of POMP resemble muscular pain disorders elsewhere in the body and it is thought that the pathophysiology of POMP may share mechanisms with entities such as regional myofascial pain, tension-type headache and fibromyalgia (FM) (Benoliel and Sharav, 2008) (Mense, 2003).

Structural and mechanistic concepts of TMD aetiology remain unproven but widely publicized. Research in the late 50s attempted to shift attention from the TMJ to the muscles of mastication. Early studies also emphasized the contribution of psychological factors to TMD leading to the psychophysiological theory. It was hypothesized that parafunctional activities aimed at relieving psychological stress led to muscle fatigue, spasm and pain.

Early pathophysiological theories offered 'one cause, one disease' hypotheses, but accumulating data indicate a more complex aetiology. New theories were subsequently proposed combining stress and occlusal disharmonies but the focus remained on occlusal adjustment as preferred therapy. The most popular current concepts are the multifactorial (Okeson, 1996; Woda and Pionchon, 1999) and biopsychosocial (Dworkin and Burgess, 1987) theories. Both of these concepts propose a complex interaction between environmental, emotional, behavioural and physical factors and have increased our understanding of the factors involved at a population or group level. Specific risk factors involved may or may not be active in any given case and therefore these concepts do not explain why the individual patient develops POMP.

Some aetiological factors have received wide acceptance. A proportion of acute muscle pain patients report a clear association with trauma. In persistent cases the initiation of pain is also often associated with a history of trauma but its exact role in the process is unclear. Importantly, however, psychological status and psychosocial functioning of the patient have emerged as central in determining the establishment of POMP and its treatment response (Suvinen *et al*, 2005).

In the following section current thinking on possible factors is reviewed that may be active in the initiation and maintenance of persistent muscle pain. It will become clear to the reader that there is evidence that the pathophysiology of POMP involves multiple mechanisms at the level of the muscles, the peripheral nervous system and the central nervous system (CNS).

Nervous system alterations in POMP patients

Pain modulation. Quantitative sensory testing studies frequently reveal evidence for abnormal somatosensory processing in POMP patients (Pfau *et al*, 2009). Large myelinated fibre hypersensitivity was shown in the skin overlying TMJs in patients with clinical pain and TMJ pathology (Eliav *et al*, 2003). However, patients with POMP demonstrated superficial (skin) large myelinated nerve fibre hyposensitivity (Eliav *et al*, 2003). Similarly, POMP patients show higher detection, discomfort and pain thresholds (decreased sensitivity) to stimuli applied to the skin over the masseter muscle (Hagberg *et al*, 1990). Within the patient group, those with the greatest spontaneous pain had the lowest threshold values. Impaired vibrotactile function and discrimination from the skin overlying muscles in POMP patients has been shown (Hollins and Sigurdsson, 1998). Tonic muscular pain has been shown to induce an elevation of detection threshold to graded monofilaments both in the affected and in the contralateral side, suggesting involvement of central mechanisms (Stohler *et al*, 2001). In contrast lowered pressure-pain thresholds (PPTs) in deep tissues have been consistently reported in POMP patients, suggesting peripheral sensitization of muscle nociceptors (Hedenberg-Magnusson *et al*, 1997; Maixner *et al*, 1998; Svensson *et al*, 2001). Because PPTs changed not only in the painful region but also at other sites, these studies also suggest central sensitization. What exactly activates the peripheral muscle nociceptor and induces muscle hyperalgesia is unclear. Stimuli may include peripheral chemical or mechanical agents, TrP activity (see below) in addition to reactive or even primary central mechanisms that may lead for example to neurogenic inflammation (Svensson and Graven-Nielsen, 2001). Experimental inflammatory conditions of the TMJ and pericranial muscles lead to changes classically associated with central sensitization which can be reversed with central delivery of *N*-methyl-D-aspartate (NMDA) antagonists (Sessle, 1999). These findings implicate central neuroplasticity in initiating and maintaining persistent muscle pain.

Altered pain regulation is suggested by findings of significantly more prevalent generalized body pain (e.g. FM and back pain) and headache in TMD patients (John *et al*, 2003). In support of this theory, TMD patients exhibit lower pain thresholds, greater temporal summation of mechanically and thermally evoked pain, stronger after sensations and multisite hyperalgesia (Maixner *et al*, 1998; Sarlani *et al*, 2004; Raphael *et al*, 2009). Patients with TMD have constantly been shown to be more pain sensitive with concomitantly reduced pain inhibition, findings similar to that of other chronic pain patients such as those with irritable bowel syndrome (King *et al*, 2009). Patients with TMD show enhanced C-fibre-mediated temporal summation to thermal stimuli applied to either the face or the forearm than control subjects and have impaired ability to discriminate stimulus frequency (Maixner *et al*, 1998). These findings further suggest a component of central hyperexcitability that contributes to the enhanced pain sensitivity observed in TMD patients. In clinical studies

about two-thirds of facial pain patients report widespread pain outside the craniocervical region (Turp *et al*, 1998). However, no generalized hypersensitivity in POMP patients has been shown in other experiments (Carlson *et al*, 1998). Thus, although some cases of POMP have multisite hyperalgesia others do not; a situation reflected in clinical experience. This may suggest two clinical and possibly therapeutic subtypes of POMP; with or without extracranial muscle involvement. Alternatively, multisite hyperalgesia may be a graded, time-dependent phenomenon (Svensson and Graven-Nielsen, 2001) and indeed experimental studies show that somatosensory sensitivity develops in the presence of experimental jaw muscle pain (Svensson *et al*, 1998b).

These data indicate generalized hyperexcitability of the CNS and generalized upregulation of nociceptive processing (decreased inhibition or increased facilitation) and suggest these may be pathophysiological mechanisms (Sarlani *et al*, 2004). In support of this hypothesis, POMP was not attenuated after peripheral noxious stimuli (ischaemic tourniquet test), which would normally activate noxious inhibitory modulation, suggesting differential or faulty recruitment of inhibitory controls (Maixner *et al*, 1995). The response of POMP patients to experimental ischaemic pain was subsequently shown to also depend on depression and somatization scores (Sherman *et al*, 2004). This suggests a complex interaction between psychosocial and biological variables in POMP patients.

Autonomic nervous system. The role of the autonomic nervous system has been investigated in persistent muscle pain, particularly FM. Although the exact pathophysiology of FM is unclear (Vierck, 2006), there is evidence for dysautonomia with increased neural sympathetic activation and a lack of an adequate sympathetic response to stressor or cardiovascular challenges (Martinez-Lavin, 2004). Additionally FM (Gracely *et al*, 2002), similar to POMP, presents features of a neuropathic pain syndrome; augmented CNS processing of pain (sensitization) and a deficit of endogenous pain inhibition (Maixner *et al*, 1995, 1998; Fillingim *et al*, 1998). The data suggests that FM may be a generalized form of sympathetically maintained neuropathic pain. Similar to that found in POMP (Galli *et al*, 2009), FM patients suffer dysfunction of the hypothalamic pituitary adrenal axis and this is thought to partly underlie sleep disorders, some pain symptoms and autonomic nervous system imbalance (Demitrack and Crofford, 1998; Drewes, 1999; Vgontzas and Chrousos, 2002; Sarzi-Puttini *et al*, 2006).

The POMP patients demonstrate increased levels of catecholamines (Evaskus and Laskin, 1972) and reduced catechol-O-methyltransferase (COMT) activity (Marbach and Levitt, 1976). In contrast, later experiments on POMP patients found that beta-adrenergic sympathomimetic stimulation did not influence pain/-pressure thresholds or electromyographic activity in the masseter and trapezius muscles or pain/pressure thresholds (Reid *et al*, 1996). In light of the evidence on the connections between the beta-adrenergic system, COMT and POMP (Nackley *et al*, 2007; Light *et al*, 2009), it is reasonable to assume that future research will demonstrate involvement of sympathetic dysfunction in POMP patients.

POMP and neuropeptides

Little is known about pain and inflammatory mediators or neuropeptides in muscle. Serotonin and prostaglandin-E2 are involved in the development of pain and hyperalgesia/allodynia of the masseter muscle in patients with FM, whereas local myalgia (myofascial pain) seems to be modulated by other, as yet unknown mediators (Kopp, 2001). The injection of neuropetides into muscle and the resultant changes may give an important insight into the cascade of events that lead to persistent muscle pain. Inclusion of male and female subjects has also allowed the analysis of gender differences.

The injection of mustard oil into rat masseter muscle resulted in pain (as assessed by immunohistochemistry) and swelling. The results of this sophisticated experiment led the authors to conclude that peripheral NMDA receptors contribute to nociceptive processing from craniofacial muscles (Ro *et al*, 2004). In a further study, the potential role of peripheral group I metabotropic glutamate receptors (GluR1) in the development of muscular hypersensitivity was investigated (Lee and Ro, 2007). GluR1 agonists increased muscle sensitivity that could be blocked by pre-emptive delivery of a GluR1 antagonist or the inhibition of protein kinase C (PKC) isoforms. Injection of glutamate into muscle is indeed painful (Cairns *et al*, 2002a, 2003a,b). Collectively, this provided support for the importance of GluR1 in muscle pain, and that PKC activation is required for their modulatory effect in craniofacial muscle tissue.

The injection of glutamate into the masseter muscle or the TMJ of the rat induced significantly greater muscle activity in female rats (Cairns *et al*, 2002b). Gonadectomy significantly reduced the magnitude of muscle activity in female rats following glutamate injection into the TMJ, a phenomenon partially reversible by the delivery of oestrogen (Cairns *et al*, 2002b). Glutamate excites and sensitizes rat masseter muscle afferent fibres through activation of peripheral excitatory amino acid receptors and resultant afferent fibre activity is greater in female than in male rats (Cairns *et al*, 2002a), an effect observed in human subjects as well (Cairns *et al*, 2001). These studies clearly demonstrate that there are gender-related differences in glutamate-evoked jaw muscle activity that are female sex hormone dependent.

Selected insight into the sensitivity of muscles to palpation (allodynia) has been obtained by extensive experiments from Svensson's group. The powerful effects of nerve growth factor (NGF) on muscle sensitization have been demonstrated (Svensson *et al*, 2003, 2008 a,c, 2010; Mann *et al*, 2006), including its gender selective effects (see below). These experiments indicate that human NGF-induced sensitization of masseter nociceptors results, in part, from the activation of

tyrosine kinase receptor. In contrast to the above experiments on pain, muscle sensitivity does not appear to be mediated through enhanced peripheral NMDA receptor activity.

In a study examining the levels of serotonin in masseter muscle in a heteregonous group of FM and POMP patients, it was found that serotonin is present in the human masseter muscle in steady state and that it is associated with pain and allodynia. The origin of the serotonin seems partly to be the blood, but their results indicate that peripheral release also occurs (Ernberg *et al*, 1999).

Of course, although most of these experiments are performed with one substance the *in vivo* milieu will include the interaction between a number of neuropeptides and amines that may act synergistically to increase sensitivity and pain in muscle (Wang *et al*, 2010). Beyond elucidating mechanisms and gender differences, these studies also serve to uncover novel therapeutic targets in the treatment of POMP.

Gender

The effects of gender on the epidemiology of pain syndromes and on pain thresholds have been extensively reported; see (Riley *et al*, 1998, 1999; Dao and LeResche, 2000; Fillingim, 2000, 2002). Women also suffer significantly more from migraines, tension-type headaches, and FM. Back pain, headache and TMD-related pain increase significantly with increasing pubertal development in girls (LeResche *et al*, 2005a). In addition female TMD patients generally have more severe physical and psychological symptoms than do men (Levitt and McKinney, 1994) and may partly explain why most studies also report that the vast majority of patients (up to 80%) who seek treatment are females (LeResche, 1997; White *et al*, 2001; Anastassaki and Magnusson, 2004). There is a female preponderance of POMP signs and symptoms (Jensen *et al*, 1993; LeResche, 1997; Magnusson *et al*, 2000). The POMP and related symptoms appear to improve over the course of pregnancy and is not paralleled by improvements in psychological distress (LeResche *et al*, 2005b). This is most likely associated with the dramatic hormonal changes occurring during pregnancy. The POMP pain in females is highest at times of lowest oestrogen and may also be related to periods of rapid oestrogen change (LeResche *et al*, 2003).

Under experimental conditions females consistently demonstrate a lowered pain threshold often affected by the stage of the menstrual cycle and by exogenous hormones such as oral contraceptives (Fillingim and Ness, 2000). Both hormone replacement therapy and use of oral contraceptives have been associated with an increased risk of TMD (LeResche *et al*, 1997; Dao *et al*, 1998) – although other reports failed to confirm this association (Hatch *et al*, 2001; Benoliel *et al*, 2011). The PPTs of muscles in female POMP patients increased significantly by 16–42% in the follicular and luteal phases but remained low in the perimenstrual phase (Isselee *et al*, 2002). The pain ratings did not correspond with PPTs and could not predict the cycle phases so that the precise relationship between pain and the menstrual cycle was unclear.

There is evidence that oestrogen and NGF may interact in the regulation of nociceptive processes. When NGF was systemically administered to healthy human subjects muscle pain particularly in the craniofacial region was observed but was more pronounced in females than in males (Petty *et al*, 1994). Interactions between NGF and oestrogen have been shown (Gollapudi and Oblinger, 1999) but the mechanisms involved in POMP are unclear.

Experimental chewing in POMP patients causes increased pain (Farella *et al*, 2001; Gavish *et al*, 2002). In a similar experiment comparing male patients with female patients, gender differences in chewing-induced pain were found in control subjects but not in patients, suggesting greater susceptibility in females (Karibe *et al*, 2003). Recent experimental studies have shown that ovarian steroids are able to regulate neuropeptides, particularly neuropeptide Y and galanin, in trigeminal ganglia (Puri *et al*, 2005). These neuropeptides are involved in pain pathways and in neuronal reaction to injury and may partly explain gender differences in various craniofacial pains including POMP.

In a study examining progression to chronicity in acute TMD patients, significant differences between genders were observed (Phillips *et al*, 2001). Overall more psychosocial distress was present in all patients progressing to chronicity but specifically females with a muscle disorder were extremely likely to become persistent pain sufferers. Further applications of gender differences in TMD remain unclear. In addition to gender specific interactions between neuropeptides and hormones, the continued accumulation of knowledge pertaining to gender-related changes in pain sensitivity and analgesic use might elucidate further pathophysiological mechanisms.

Ethnicity

Anthropologists and biologists are increasingly defining race as a social construct and not solely a scientific category (Morris, 2001). Cultural and social factors are the foundation for the expression and management of pain (Lasch, 2002), and it is important to appreciate cultural factors that influence healthcare workers. Ethnocultural background may influence a clinician's assessment of pain intensity in patients (Ng *et al*, 1996; Sheiner *et al*, 1999), and minorities may be at risk for inadequate pain control (Lasch, 2002). Therefore, we must be aware of the cultural factors that affect the way patients respond to pain and its management, as well as understand the way in which the 'ethnicity' of clinicians and patients may influence healthcare delivery.

The cultural and possibly genetic effects of persistent TMD pain on patient behaviour has also been recently highlighted (Reiter *et al*, 2006). In spite of no differences in the physical parameters of RDC TMD diagnosis (Axis I) there were significant differences between two distinct ethnic populations in their psychosocial response (Axis II). This suggests that cultural differences

in attitudes to health and disease affect coping abilities and suffering in patients with TMD.

Trauma

It has been increasingly recognized that trauma to the craniofacial region may lead to POMP (Fischer *et al*, 2006). Trauma can be classified as macrotrauma (e.g. head injury) or microtrauma (e.g. dental treatment) (Huang *et al*, 2002). The exact mechanisms how these result in POMP are unclear but may include direct/invasive muscle damage, stretch injuries to muscle or long-term immobilization of fractured jaws. Indirect injury of brain tissue may lead to persistent head and face pain although there is no correlation between degree of injury the incidence and severity of pain. Shear forces applied to the brain may result in damage. Following even relatively minor head trauma progressive and extensive axonal injury due to widespread shearing occurs and is commonly known as diffuse axonal injury (Inglese *et al*, 2005; Povlishock and Katz, 2005). A history of trauma is present in a significant number of patients with TMD (Pullinger and Seligman, 1991; Macfarlane *et al*, 2001, 2003a; Huang *et al*, 2002; Velly *et al*, 2003; Fischer *et al*, 2006), see also review (Freund and Schwartz, 2002). Dental surgery has been found to increase the prevalence and symptomatology of TMD (Plesh *et al*, 1999).

Whether posttraumatic TMD patients suffer more severe symptoms or are more resistant to treatment is unclear (De Boever and Keersmaekers, 1996; Kolbinson *et al*, 1997b; Steed and Wexler, 2001). There are indications that early intervention with a conservative approach (physical therapy, tricyclics, and non-steroidal anti-inflammatory drugs) significantly improves prognosis of posttraumatic cases (Benoliel *et al*, 1994).

Cervical injury

Indirect neck trauma, as in hyperextension-flexion injury to the cervical complex (whiplash), commonly results in acute neck pain, see (Spitzer *et al*, 1995; Cote *et al*, 2000; Solomon, 2005). The persistence of neck pain is not consistently related to the degree of trauma or cervical pathology. There are many patients with structural cervical lesions who suffer no pain (Solomon, 2005).

Whiplash has been implicated in the aetiology of TMD (Klobas *et al*, 2004), but how it may lead to POMP is unclear. Moreover, many studies assess the presence of TMD (includes both POMP and TMJ disorders) (Carroll *et al*, 2007) or solely assess the TMJ (Sale *et al*, 2010) making the interperatation of the literature difficult. Dynamic three dimensional modelling shows little evidence to support the contention that there is damage to the masticatory apparatus during whiplash (Perez del Palomar and Doblare, 2008). Moreover, it has been suggested that whiplash may lead to widespread body pain and that TMD may just be one expression rather than a specific outcome of whiplash (Visscher *et al*, 2005).

A possible association between TMD and whiplash has beeen suggested with some studies showing resultant functional impairment of the masticatory apparatus in patients with a history of whiplash (Haggman-Henrikson *et al*, 2002, 2004; Eriksson *et al*, 2004; Gronqvist *et al*, 2008). However, long-term follow-up of whiplash patients does not indicate an increased risk for persistent TMD (Barnsley *et al*, 1994; Ferrari *et al*, 1999; Kasch *et al*, 2002). The role of litigation in persistence of chronic whiplash pain is unclear (Burgess, 1991). One study has shown that when compensation for pain and suffering is eliminated there is a decreased incidence and improved prognosis of whiplash injury (Cassidy *et al*, 2000). This has not been universally demonstrated (Burgess and Dworkin, 1993; Kolbinson *et al*, 1996, 1997a). Cultural or regional differences, possibly based on health beliefs, may also play a role; for example, Lithuanian accident victims do not appear to report persistent symptoms of TMD despite their acute whiplash injuries (Ferrari *et al*, 1999). Some studies have positively confirmed the comorbidity of POMP and neck pain (Ciancaglini *et al*, 1999). This may be a confounder as one of the features of POMP is neck muscle pain. Moreover, in general, headache and facial pain patients report concomitant cervical pain and vice-versa; probably due to convergence of trigeminal and cervical afferents on second order neurons in the brainstem trigeminocervical complex. This bidirectionality of pain referral has been experimentally demonstrated (Ge *et al*, 2004). However, trigeminally and cervically innervated muscles have significantly different patterns of spread and referral of pain so that the bidirectionality is not equal in pattern or potency (Schmidt-Hansen *et al*, 2006). In summary there is insufficient substantial clinical data to support a causative role for whiplash in TMD/POMP (Kolbinson *et al*, 1997b).

Psychosocial factors

Persistent pain, from whatever source, is in many patients associated with psychological distress and psychosocial disturbances. These levels of distress may significantly impact on patient compliance and treatment outcomes. Indeed, although a minority of TMD patients will manifest significant psychological distress and psychosocial disturbances, the level of distress often predicts treatment demand and outcome (Epker and Gatchel, 2000; Raphael *et al*, 2000). Patients with persistent pain who seek treatment usually have more severe pain, distress and a poorer prognosis. Thus, although psychosocial factors are not seen as aetiological factors in TMD they have an important role in treatment response and transition to chronicity. Several methods have been designed to measure the emotional results of stress or the intensity of environmental stress. These methods are employed as secondary endpoints in the assessment of outcomes in the treatment of chronic pain. The methodologies have recently been reviewed and the Beck Depression Inventory or the Profile of Mood States questionnaire is recommended for the assessment treatment outcomes and for research in chronic pain (Dworkin *et al*, 2005). For TMD the RDC TMD axis II criteria have been extensively applied.

Currently, psychosocial factors are considered important variables in POMP. Patients with POMP are frequently found to suffer from other stress-related disorders such as migraine, backache, nervous stomach and gastrointestinal ulcers (Turp *et al*, 1997; Korszun *et al*, 1998; Aaron and Buchwald, 2003). POMP patients consistently suffer higher levels of distress than articular TMD (Galdón *et al*, 2006; Ferrando *et al*, 2004).

Depression and lack of sleep have been found to be significantly increased in TMD patients (Carlson *et al*, 1998; Garofalo *et al*, 1998; Epker *et al*, 1999; Macfarlane *et al*, 2001; Vazquez-Delgado *et al*, 2004; Selaimen *et al*, 2006). Depression and chronic widespread pain are significant risk factors for the onset of POMP (Velly *et al*, 2010). Cognitive coping abilities in response to injury and pain are also thought important in TMD. Two aspects of coping emerge as therapeutically relevant in TMD; control or adjustment in response to pain and the recruitment of maladaptive coping strategies such as catastrophising in an attempt to control pain (Suvinen *et al*, 2005). A positive response to TMD treatment has been correlated to increased coping abilities (Schnurr *et al*, 1991).

Studies suggest that stress-related disorders may underlie or contribute to the development of TMD chronicity and may therefore be viewed as perpetuating rather than initiating factors (Carlson *et al*, 1998; Garofalo *et al*, 1998; Epker *et al*, 1999; Macfarlane *et al*, 2001). Dysregulation in terms of enhanced negative feedback suppression of the hypothalamic pituitary adrenal axis exists in chronic myogenous facial pain. These results suggest a more central aetiology with dysregulations in the stress and pain modulating system (Galli *et al*, 2009). Indeed, TMD patients with increased self-efficacy measures suffered lower levels of pain, disability or psychological distress and reported greater use of an active, adaptive pain-coping strategy (Brister *et al*, 2006). These findings form the basis for biobehavioural interventions.

Occlusion

Bruxism connection. The relation between occlusion and POMP is based on the vicious cycle theory where an occlusal interference is supposed to induce hyperactivity and spasm of the affected muscle, which in turn leads to ischaemia secondary to blood vessel compression. Ischaemic contractions are painful and activate muscle nociceptors; by this mechanism the vicious cycle is closed. Whilst the extent of the occlusal 'interference' may be minute it supposedly upsets proprioceptive feedback and triggers bruxism with spasm of masticatory muscles. These assumptions have been refuted by experiments demonstrating that artificial occlusal discrepancies tend to reduce bruxism rather than enhance it (Rugh *et al*, 1984) and by the lack of correlation between oral parafunctions and pain intensity in TMD patients (van der Meulen *et al*, 2006; Svensson *et al*, 2008b). Clinically no correlation has been found between bruxism and muscle tenderness (Pergamalian *et al*, 2003), see above.

Prerequisites for such an aetiology would be that POMP patients demonstrate persistently elevated activity of masticatory muscles at rest and show a consistent relation to malocclusion. Although electoromyography (EMG) activity recorded from masticatory muscles in some patients is higher, later studies have shown that this activity fails to accurately define patients *vs* controls (Glaros *et al*, 1997).

Occlusal structure and POMP. Several long-term follow-up studies have also shown no consistent pattern between occlusal variables and TMD (Clark *et al*, 1999; Carlsson *et al*, 2002), although some show weak associations (Magnusson *et al*, 2005). Some rare malocclusions were associated with signs or symptoms of TMD: unilateral open bite, negative overjet, and unilateral scissors-bite in men, and edge-to-edge bite in women. However, malocclusions (and functional occlusion factors) accounted for only a small part of the differences between the control population and the study population with signs or symptoms of TMD (Henrikson and Nilner, 2003; Gesch *et al*, 2004a). In line with these findings, deep bite patients more frequently reported jaw stiffness, muscle disorders (Sonnesen and Svensson, 2008). Interestingly, somatization scores were significantly higher in the deep bite group compared with those of the controls. These findings suggest that a deep bite, in particular with retroclined upper incisors, can represent a risk factor for TMD (Sonnesen and Svensson, 2008). One article reported that waketime non-functional tooth contact occurred more frequently in POMP patients than in controls (Chen *et al*, 2007). However, the study was based on patients reporting at preset times whether their teeth were in contact or not. The POMP patients were also found to have higher perceived stress scores. In view of these one wonders whether the tooth contact may not be a result of stress or of muscle dysfunction resulting from pain. In patients awaiting full dentures no statistically significant correlations were found between signs and symptoms of TMD and occlusal errors or freeway space (Dervis, 2004). Recent studies have avoided the issue of muscle hyperactivity and examined the effects of acute artificial occlusal interferences on parameters such as facial pain, chewing ability and jaw fatigue (Le Bell *et al*, 2006). Acute malocclusions will cause extreme discomfort, however, this experimental design does not parallel the clinical situation in POMP patients where purported malocclusions occur slowly and are accompanied by skeletal growth and adaptation. Indeed the effects in these studies were most prominent on occlusal discomfort and chewing problems with TMD patients showing reduced adaptation (Le Bell *et al*, 2006). Their results show that the TMD patients undergoing placebo intervention also had a tendency to develop mild symptoms; in some cases comparable to the non-TMD population with active interferences (Le Bell *et al*, 2006). This would seem to indicate that TMD patients have less adaptive capabilities to both active and control interventions but leaves the precise relationship between TMD-pain and occlusion unanswered.

Studies show no occlusal factors to be consistently associated with TMD onset and no malocclusion is able to accurately predict TMD incidence (Gesch *et al*, 2004b, 2005; Pahkala and Qvarnstrom, 2004). Taken together the data indicates that occlusal factors seem to be of minor (if any) importance in the aetiology of TMD.

Skeletal morphological features
The association between certain skeletal morphological features and the prevalence of TMD has been the focus of much controversy. Most research has focused on derangements of the TMJ as they relate to skeletal morphology. Little data is available on POMP (Farella *et al*, 2003). Vertical craniofacial height has been found to affect pain onset in endogenous pain models. Nevertheless, data presented in early reviews and in recent research indicate that the distribution of major skeletal/occlusal categories in TMD patients does not differ significantly from the normal population (Greene and Marbach, 1982) and that no single skeletal/occlusal problem can accurately predict TMD onset (Egermark *et al*, 2001; Mohlin *et al*, 2004).

Orthodontics
The possibility that orthodontic treatment in any of its many forms may lead to the initiation or deterioration of TMD is of great concern (Michelotti and Iodice, 2010). Recent research suggests that orthodontics does not entail an increased risk for developing either signs or symptoms of TMD (Egermark *et al*, 2001, 2005; Kim *et al*, 2002; Henrikson and Nilner, 2003; Mohlin *et al*, 2004; Hirsch, 2009; Macfarlane *et al*, 2009; Luther *et al*, 2010). Therefore, and based on the existing data, the relationship of TMD to occlusion and orthodontic treatment is minor. One of the major epidemiological confounders was underlined in a systematic review (McNamara *et al*, 1995). This review concluded that since signs and symptoms of TMD occur in healthy individuals and increase with age, particularly during adolescence, TMD that originate during various types of dental treatment may not be related to the treatment but may be a naturally occurring phenomenon (McNamara *et al*, 1995).

Moreover, in meta-analyses no study was found indicating that traditional orthodontic treatment increased the prevalence of TMD (Kim *et al*, 2002; How, 2004). Some mild signs such as soft click or tenderness on palpation were occasionally reported but these are difficult to accurately assess and asymptomatic clicks are considered physiological. The occlusion and the TMJ are important factors in successful orthodontic treatment and stability; once again the question remains as to the connection between these and TMD. Evidence suggests that there is very little if any scientific evidence to support this connection.

Orthodontic therapy aimed at improving TMD has largely no supporting data (Macfarlane *et al*, 2009; Luther *et al*, 2010), apart from correction of unilateral openbite that has a weak association with TMD improvement, but this needs further confirmation (McNamara, 1997).

The temporomandibular joint
Theoretically, trauma or noxious stimulation of TMJ tissues can produce a sustained excitation of masticatory muscles that may serve to protect the masticatory system from potentially damaging movements and stimuli (Sessle and Hu, 1991). Clinically, the frequent comorbidity of arthralgia and myalgia (Huang *et al*, 2002) has led to such hypotheses linking their etiologies, but these have not been proven (Schiffman *et al*, 1992). Such comorbidity may reflect sensitization and referral patterns mediated by primary afferents in the TMJ and muscles of mastication cosynapsing on dorsal horn neurons (convergence). Moreover, experimental injection into the TMJ of algesic chemicals resulted in sustained reflex increase in EMG activity of jaw-opening muscles; excitatory effects were also seen in jaw-closing muscles but were generally weaker (Broton and Sessle, 1988). While such effects may be related to clinically based concepts of myofascial dysfunction (e.g. splinting, myospastic activity and TrP), the weak effects in jaw-closing muscles and the stronger effects in antagonist muscles suggest associations more in keeping with protective, withdrawal-type reflexes (Sessle and Hu, 1991). Based upon the present available data it seems that pain originating in the TMJ contributes minimally to the development of POMP.

Parafunction
Muscle hyperactivity and bruxism. A thorough understanding of bruxism is essential to fully appreciate the implications of the ongoing debate relating to its role in the pathophysiology of POMP, see (Bader and Lavigne, 2000; Lavigne *et al*, 2001; Kato *et al*, 2003; Winocur *et al*, 2003; Ahlberg *et al*, 2004). The aetiology of sleep bruxism is probably related to changes in the central/autonomic nervous system that may be modulated by stress (Kato *et al*, 2003). The aetiology of wake bruxism is unclear and may involve stress in predisposed individuals.

Effects of bruxism. Bruxism may cause muscle hypertrophy and severe damage to the dentition. The parafunctional forces applied during bruxism have also been suggested in the aetiology of dental implant failure, periodontal tissue damage and tooth fracture. Hypothetically the repetitive overloading of the TMJ and muscles by bruxing movements may cause tissue damage leading to TMD. It is possible that muscle overload may initiate or reactivate TrP in susceptible individuals.

In order to be able to establish a cause and effect relationship between bruxism and POMP the evidence needs to be examined with several criteria as basic tenets; bias, chance and confounders are absent, the association is consistent, bruxism must precede POMP, some type of relation exists between the degree of bruxism and the severity of the POMP (i.e. a dose–response) and the association makes epidemiological sense (Lobbezoo and Lavigne, 1997). We will presently examine whether occlusal discrepancies induce muscle

hyperactivity and if occlusal discrepancies or muscle hyperactivity can cause POMP.

Bruxism and orofacial pain. Excessive bruxism with insufficient relaxation, as in jaw clenching, is thought to lead to muscle ischaemia and pain. In this context the most widespread belief is that POMP is induced by repetitive tooth clenching, grinding or abnormal posturing of the jaw. These habits are, however, extremely common and statistically have not been proven to induce POMP. Evidence for masticatory muscle hyperactivity in the aetiology of POMP is largely indirect, and relies mostly on experimental tooth clenching.

Masticatory muscle pain has been studied experimentally using two general approaches. Exogenous models of pain involve the injection of algesic substances into muscle and are discussed later in this section. Endogenous models of experimental pain have been studied extensively and involve the persistent contraction or exercise of masticatory muscles (Christensen, 1971, 1981; Scott and Lundeen, 1980; Clark *et al*, 1984, 1991; Bowley and Gale, 1987; Choy and Kydd, 1988; Buchner *et al*, 1992; Gay *et al*, 1994; Lund and Stohler, 1994; Svensson and Graven-Nielsen, 2001; Turp *et al*, 2002; Shiau *et al*, 2003; Ariji *et al*, 2004; Glaros and Burton, 2004). These experiments have produced inconsistent, non-specific and inconclusive results questioning the role of muscle hyperactivity/overload in POMP.

Obviously these intensive experimental exercises are not identical to the chronic parafunctional activities, which occur in patients. For example chronic low level clenching induces muscle pain but again only in a subset of patients (Glaros *et al*, 1998). Population studies suggest that tooth grinding may cause myalgia (Macfarlane *et al*, 2001, 2003b; Lobbezoo *et al*, 2006). It has also been found that self reported clenching is more consistently associated with POMP than grinding although there was no cause and effect relationship established (Velly *et al*, 2003). The reliability of self reported bruxing habits is problematic; 85–90% of the population will report that at some time they have ground or clenched their teeth (Bader and Lavigne, 2000). Many patients who self report tooth grinding admit that this was first brought to their attention by their dentist (Marbach *et al*, 1990). The reliability of clinician judgements of bruxism has been found to be extremely poor (Marbach *et al*, 2003). Notwithstanding, self reported clenching is frequently associated with POMP (Huang *et al*, 2002; Johansson *et al*, 2006). However, the directionality of a possible cause and effect remains unproven and in addition bruxism and POMP may be clinical manifestations of a shared neuropathology.

Whilst the models described have not totally elucidated the mechanisms underlying POMP they have consistently shown that pain following experimental muscle contraction is of short duration and self-limiting. Thus, sustained or repeated abnormal loading of the masticatory apparatus as in these experiments is of a doubtful primary role in POMP.

If muscle hyperactivity is clearly related to POMP, bruxers should report more muscle pain. Some preliminary results suggest that a majority of patients with bruxism have pain levels and sleep quality comparable with POMP patients (Lavigne *et al*, 1991). Myalgia is reported in only 20–30% of bruxers and it unclear if this is a myofascial pain or a form of post exercise muscle soreness (PEMS) (Lavigne *et al*, 1996; Bader and Lavigne, 2000). Recent studies show that only gender, joint clicking and other non-painful TMD symptoms are significantly related to nocturnal EMG activity or bruxism (Ahlberg *et al*, 2004; Baba *et al*, 2005). Moreover, 19.7% of POMP patients report peak pain in the morning whilst in bruxers this is 83.3%, suggesting that the latter may indeed be a form of PEMS (Lavigne *et al*, 1996; Camparis and Siqueira, 2006). In addition, the bruxers with morning pain have less tooth-grinding episodes than those without (Bader and Lavigne, 2000; Rompre *et al*, 2007). This may be due to a protective mechanism that reduces muscle activity in the presence of pain. Alternatively the high bruxers with no pain may have undergone an adaptive process (Bader and Lavigne, 2000). Comparing bruxers with and without TMD no significant differences in bruxism levels or sleep patterns were present (Camparis *et al*, 2006). In contrast a study on adult bruxers revealed frequent complaints of orofacial and bodily pain and 65% reported frequent headaches in the morning (Bader *et al*, 1997). However, the patients in this study (Bader *et al*, 1997) reported more comorbid features such as anxiety and tension than those in previous studies (Lavigne *et al*, 1996).

In summary, available data do not support the traditional concept of POMP induced or maintained by muscle hyperactivity (Lund *et al*, 1991). Moreover, examining the available data *vis-a-vis* the ideal criteria for establishing a cause and effect relationship casts serious doubts on the validity of the hypothesis that muscle hyperactivity leads to POMP. Bias and confounders such as anxiety, EMG activity from the muscles of facial expression and the separation of rhythmic masticatory muscle activity from actual grinding or clenching are not consistently excluded or accounted for. Daytime or sleep bruxism may be different in their effects on the masticatory system but these have not been separated in studies. The association between bruxism and POMP is inconsistent; experimental models show a high degree of selectivity and no prolonged muscle pain. No dose–response is present as demonstrated by the facts that bruxers do not report extremely high levels of POMP and high activity bruxers in fact complain less of morning muscle pain than do low level bruxers. Finally the association makes little epidemiological sense; TMD are rare in children in whom bruxism is most common and TMD/POMP peaks in young adults when bruxism is shown to be decreasing in frequency. There is little evidence to support SB in the aetiology of POMP but the role of bruxing and clenching habits particularly in the daytime are as yet unclear (Lobbezoo *et al*, 2006). In addition, we have little data on the ability of such bruxing habits to activate or initiate TrP in masticatory muscles in a

similar way that has been suggested for myofascial pain in other regions (Simons, 2004). Based on the above the vicious cycle theory is untenable and an alternative model is needed to explain motor changes in patients with muscle pain and disorders.

The pain-adaptation model. The pain-adaptation model is based on data from persistent musculoskeletal pain conditions (including that of POMP) and proposes that the observed changes in motor function are secondary to persistent pain and mediated at the spinal level (Lund *et al*, 1991). Changes in masticatory muscle function, secondary to experimental muscle pain as described above, support this model and confirm clinical complaints of dysfunction in muscular TMD patients (Svensson and Graven-Nielsen, 2001). Injection of hypertonic saline into the jaw muscles induces pain with a significant reduction in jaw movements and in EMG activity during the agonist phase accompanied by a small increase in antagonist muscle activity (Graven-Nielsen *et al*, 1997; Svensson *et al*, 1998a). The pain-adaptation model suggested that pain will induce inhibition of alpha motorneurons during jaw closing and facilitate these during antagonist (opening) activity (Lund *et al*, 1991). This model therefore accurately fits the currently available data. More recently the 'Integrated Pain Adaptation Model' has been suggested (Murray and Peck, 2007) which proposes that the existing Pain Adaptation Model is a subset of a broader model that could be called the Integrated Pain Adaptation Model. This model is based on the premise that pain acts as a homeostatic emotion requiring a behavioural response; an optimized recruitment strategy of motor units that represents the individual's integrated motor response to the sensory-discriminative, motivational-affective and cognitive-evaluative components of pain. This recruitment strategy aims to minimize pain and maintain homeostasis.

If muscle dysfunction is not the cause of pain but rather part of the spectrum of a 'pain-adaptation' response then some of the parafunctions including some of the bruxing habits can no longer be considered as a primary aetiological mechanism of pain in POMP (Lund *et al*, 1991). However, the precise association between bruxism and POMP remains unclear at this stage.

Trigger points and the sympathetic nervous system
Myofascial pain whether in the facial area, head or other body parts is often characterized by the presence of TrP (Gerwin *et al*, 2004; Simons, 2004). It is thought that muscular pain arises from TrP and indeed in many POMP patients pressure on a TrP will activate intense pain and induce referral to characteristic sites. The muscle around a TrP is usually hard and may be nodular or appear as a taut band. Data suggest that TrPs are found in the area of the neuromuscular junction at the motor end plate. Tonical activity results in localized contraction that together with adjacent active end plates, contribute to the formation of the taut band or nodule (Gerwin *et al*, 2004). The continuous electrophysiological activity of motor endplates is secondary to unchecked release of acetyl-choline. Endplate activity or noise is significantly more common in myofascial pain patients than in controls. Continued contraction in the area of TrPs leads to localized hypoxia (hypoperfusion), lowered pH and the accumulation of proinflammatory mediators (Simons, 2004; Shah *et al*, 2005). Lowered pH increases the activity of peripheral receptors including the vanilloid receptor further sensitizing muscle nociceptors (Mense, 2003). This localized contraction in TrPs is not however, associated with generalized muscle hyperactivity so that this should not be confused with the muscle hyperactivity theory. The appearance of active TrPs is thought to be related to muscle trauma particularly eccentric muscle lengthening during contraction (Gerwin *et al*, 2004). However, experiments directed at inducing such damage have largely been inconclusive.

It has been suggested that muscle hypoperfusion may be the primary factor in initiating muscle pain, possibly due to changes in sympathetic control (Maekawa *et al*, 2002). Moreover, the unchecked motor endplate activity described above develops sensitivity to sympathetic nervous system activity (Gerwin *et al*, 2004). Similarly sensitized nociceptors may be activated by sympathetic activity. Thus, the sympathetic nervous system is capable of independently initiating all the features of POMP (Maekawa *et al*, 2002; Mense, 2002). There is insufficient data at present to entirely endorse or refute this hypothesis.

Life style
Very little research has been performed on the relationship between various lifestyle habits such as nutrition, exercise and smoking on the presence and treatment of POMP. In a patient population current tobacco use was associated with unfavourable demographic variables and more pain interference in TMD subjects, but these effects were less pronounced in cases of myofascial pain (Weingarten *et al*, 2009). Cigarrete smoking and its extent has been positively correlated with pain intensity in TMD patients, with no differences between articular pain and POMP (Melis *et al*, 2010). In a recent, population-based questionnaire study current tobacco use was significantly higher in POMP patients relative to TMJ or controls (Benoliel *et al*, 2011). The same authors reported that maintaining an organized nutritional schedule was found significantly less frequently in POMP cases (Benoliel *et al*, 2011).

Genetics
No heritability has been found in humans for any TMD. No concordance in TMD signs and symptoms was found in a study on monozygotic and dizygotic twins (Michalowicz *et al*, 2000). A study on female POMP patients and their first degree relatives revealed no evidence that there is any familial aggregation (Raphael *et al*, 1999). However, genetic influences on TMD development have been shown (Diatchenko *et al*, 2005; Ojima *et al*, 2007). A significant association between polymorphisms in the serotonin transporter gene and TMD has been shown in a Japanese population (Ojima

et al, 2007). A relationship between clinical phenotype of TMD (articular *vs* non-articular) and COMT polymorphisms has been reported (Erdal *et al*, 2003) but neither the clinical criteria used nor the terminology (myofacial *vs* myofascial) are in line with current thinking. Further work on COMT identified three genetic variants (haplotypes) of the COMT-encoding gene that were designated as low pain sensitivity (LPS), average pain sensitivity (APS) and high pain sensitivity (HPS). These haplotypes encompass 96% of the human population, and five combinations of these haplotypes were shown to be strongly associated with the sensitivity to experimental pain. The presence of even a single LPS haplotype diminished, by as much as 2.3 times, the risk of developing POMP. The LPS haplotype produces much higher levels of COMT enzymatic activity when compared with the levels of APS or HPS haplotypes. Inhibition of COMT in the rat results in a profound increase in pain sensitivity. Thus, COMT activity substantially influences pain sensitivity, and the three major haplotypes determine COMT activity in humans that inversely correlates with pain sensitivity and the risk of developing POMP (Diatchenko *et al*, 2005). In a further study, examining beta-adrenergic receptor haplotypes, positive or negative imbalances in receptor function increased the vulnerability to persistent pain conditions such as TMD (Diatchenko *et al*, 2006a). The same group later showed the first direct evidence that low COMT activity leads to increased pain sensitivity via a beta-adrenergic mechanism (Nackley *et al*, 2007). The study was a major breakthrough but it must be stressed that the genetic variation in COMT seems not specific to POMP but to pain sensitivity and the development of persistent pain in general (Diatchenko *et al*, 2006b) and act also via the opioid system (Zubieta *et al*, 2003). Notwithstanding, these findings are of considerable clinical importance, suggesting that pain conditions resulting from low COMT activity and/or elevated catecholamine levels can be treated with pharmacological agents that block both beta (2)- and beta (3)-adrenergic receptors. Adrenergic dysregulation was shown in patients with TMD or FM (Light *et al*, 2009) and acute treatment with low-dose propranolol led to short-term improvement. However, the clinical effectiveness of propranolol is dependent on the COMT haplotype (Tchivileva *et al*, 2010). These studies collectively mark what must be the beginnings of pharmacogenomics in the management of orofacial pain.

Sleep disturbance

Associations between pain and sleep disturbance have been documented in several persistent pain patient samples, usually in association with depression (Ohayon, 2005; see also section on psychosocial variables). Recent research suggests bi-directional interactions between the experience of pain and the process of sleep; pain interferes with the ability to obtain sleep, and disrupted sleep contributes to enhanced pain perception. Pain severity seems to be a major parameter (Smith and Haythornthwaite, 2004). It has been recently suggested that poor sleep may interfere with endogenous pain modulation (Smith *et al*, 2007; Edwards *et al*, 2009).

Pain disturbances and pain-related awakenings are common in persistent orofacial pain and are related to pain intensity (Riley *et al*, 2001; Wong *et al*, 2008; Benoliel *et al*, 2009), see also review (Schutz *et al*, 2009).The POMP patients often report poor sleep and have been objectively shown to have poorer sleep quality than painful TMJ or chronic daily headache patients (Carlson *et al*, 1998; Lindroth *et al*, 2002; Yatani *et al*, 2002; Vazquez-Delgado *et al*, 2004). Pain-related awakenings occur in about a quarter of POMP patients and is related the degree of muscle tenderness (Benoliel *et al*, 2009). Primary insomnia was associated with reduced mechanical and thermal pain thresholds in orofacial muscles even after controlling for multiple potential confounds (Smith *et al*, 2009).

Comorbidities

Persistent orofacial muscle pain, has been significantly associated with a number of comorbidities such as irritable bowel syndrome (Grossi *et al*, 2008), FM (Korszun *et al*, 1998; Balasubramaniam *et al*, 2007; Clauw, 2009), migraine (DiPaolo *et al*, 2009; Franco

Table 2 Summary of level of evidence for individual pathophysiological factors

Level of evidence → *Factor* ↓	*Strong*	*Moderate*	*Low*	*No*
Nervous system	Endogenous pain modulation; peripheral/central sensitization	Autonomic nervous system	Neurodegenerative	
Trauma		Dental interventions; facial macrotrauma	Cervical (?)	
Demographics	Gender	Age	Ethnicity	
Psychological	Catastrophizing	Stress; depression; childhood events;	Personality disorders	Socioeconomic (?)
Dento-skeletal			Occlusion	Orthodontics
Functional			Parafunction (daytime)	
Lifestyle			Nutrition; smoking	
Sleep		Sleep disorders		Sleep bruxism
Genetics		Genotypic		Inheritable
Comorbidities/secondary	Fibromyalgia	Headache; LBP; IBS; CWSP	Infection	Secondary gain (?)

LBP, lower back pain; IBS, irritable bowel syndrome; CWSP, chronic widespread pain; ?, disputable.

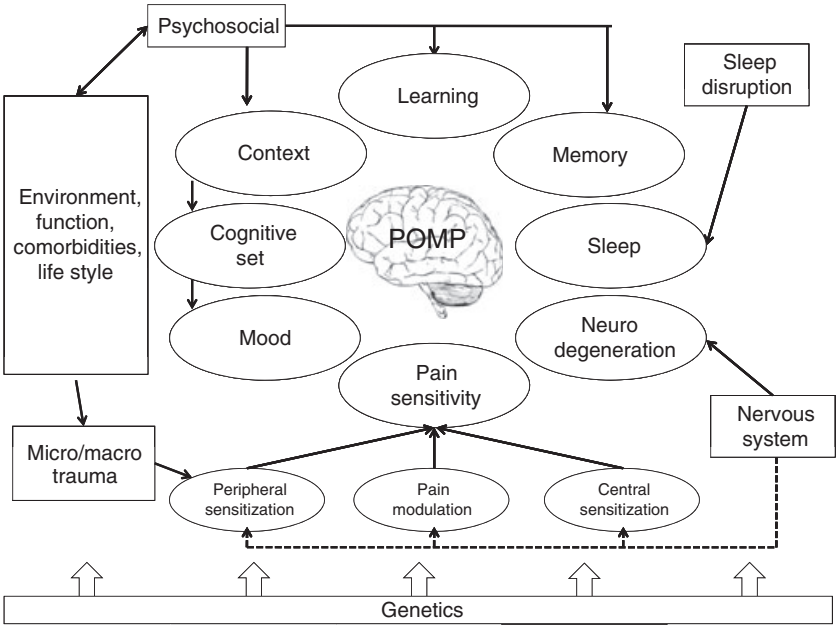

Figure 1 A complex disease model perspective of POMP. Overall POMP, like other persistent pain conditions, can be viewed as a 'gene by environment interaction' (Diatchenko *et al*, 2006c). Multiple genes have been identified, e.g. catechol-O-methyl transferase, or α-adrenoreceptor 2 (see text) which carry an increased risk for a 'higher pain sensitivity'. Environmental factors can increase the load either through psychosocial mechanisms or physical impact, e.g. trauma. The overall presentation of pain is determined by the interplay of several 'brain' factors like context, cognition, mood, learning, memory, sleep and neurodegeneration (Diatchenko *et al*, 2006c). Furthermore, biological gender and ethnicity may influence the balance between factors. POMP, persistent orofacial muscle pain

et al, 2010; Stuginski-Barbosa *et al*, 2010) and tension-type headache (Ballegaard *et al*, 2008; Goncalves *et al*, 2010). There are indications that these entities and POMP share a basic disorder in pain modulation and psychosocial factors. The study of these associations will no doubt shed light on the pathophysiology of POMP.

Summary

It is clear that many factors may be active in the aetiology of POMP, see Table 2 and Figure 1. Host susceptibility plays a role in POMP at a number of levels. Genetically influenced physical traits such as pain modulation and pharmacogenomics may then interact with psychological traits to determine disease onset and progression and indeed whether persistent pain develops. In addition, environmental parameters such as ethnicity, culture and stress are essential variables in the patient's coping abilities and demand for treatment. The effects of gender are paramount and may be expressed via interactions between hormones and nociceptive pathways as well as environmental and cultural issues.

Any of the aetiological agents discussed may contribute to POMP in one patient but not in another, who may require a single or a combination of aetiological factors to develop POMP. We are still unable to accurately identify these factors in the individual patient so as to tailor a focused, mechanism based treatment plan. Notwithstanding available treatment options are able to offer adequate management for most POMP cases.

Authors Contributions

Working meeting during which all authors brought previously prepared work (literature reviews, summaries etc.) then actively participated in intensive discussion. A manuscript 'skeleton' was prepared and written up largely by RB with much help from PS and EE. The authors then reviewed this manuscript and submitted these to me. Final review was by MG, PS and EE. Prof Doug Peterson has read over the manuscript and his suggestions have largely been incorporated. The minutes of the meeting and discussions were summarized by Gary Heir.

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