

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 (PUB-MED, Cochrane Database) of the combinations of the following terms ‘temporomandibular’, ‘facial’, ‘cranio-facial’, ‘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 successfully tested and validated (Look *et al*, 2010; Ohrbach *et al*, 2010; Schiffman *et al*,

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24 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 exacerbatated, 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 exacerbate 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

<i>Myofascial pain (AAOP)</i>	<i>Myofascial pain without/with* limited opening (RDC-TMD) Axis I: Physical findings</i>
Regional dull, aching pain Aggravated by mandibular function	Complaint of pain of muscle origin In jaw, temples, face, preauricular or auricular at rest or during function
Hyperirritable sites or trigger points Frequently found within a taut band of muscle tissue or fascia Provocation of these trigger points alters the pain complaint and reveals a pattern of referral > 50% reduction of pain is inducible by muscle stretch preceded by trigger point treatment with Vapocoolant spray, or Local anaesthetic injection	Pain associated with localized areas of tenderness to palpation in muscle 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) R/L temporalis: posterior, middle, anterior, tendon (eight sites) R/L masseter: origin, body, insertion (six sites) R/L Posterior mandibular region (2 sites) R/L submandibular region (2 sites) R/L lateral pterygoid region (2 sites)
Signs and symptoms that may accompany pain Sensation of muscle stiffness Sensation of acute malocclusion, not clinically verified Ear symptoms, tinnitus, vertigo, toothache, tension-type headache Decreased mouth opening; passive stretching increases opening by > 4 mm Hyperalgesia in the region of referred pain	Myofascial pain as above accompanied by Stiffness of muscles *Pain free un-assisted mandibular opening of < 40 mm *With assistance an increase of ≥5 mm in mandibular opening
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).

^aOther 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 (Sarlan *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 neuropeptides 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 heterogeneous 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 interpretation 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 been 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 electromyography (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 algescic 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 algescic 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; Arijii *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 motoneurons 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). Cigarette 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 Catastrophizing	Age	Ethnicity	
Psychological		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.

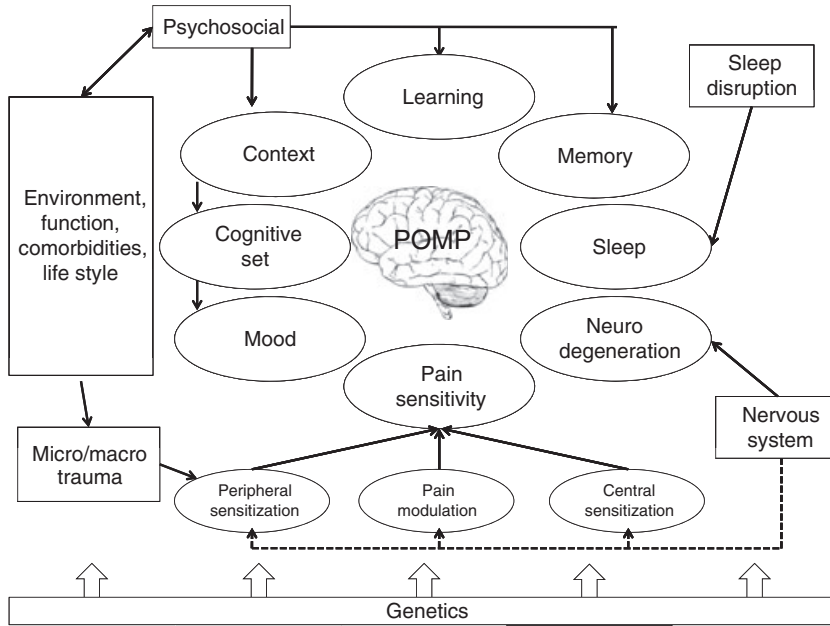


Figure 1 A complex disease model perspective of POMP. Overall POMP, like other persistent pain conditions, can be viewed as a 'gene by environment interaction' (Diatchenko *et al*, 2006c). Multiple genes have been identified, e.g. catechol-O-methyl transferase, or α -adrenoreceptor 2 (see text) which 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.

References

- Aaron LA, Buchwald D (2003). Chronic diffuse musculoskeletal pain, fibromyalgia and co-morbid unexplained clinical conditions. *Best Pract Res Clin Rheumatol* **17**: 563–574.
- Ahlberg J, Savolainen A, Rantala M, Lindholm H, Kononen M (2004). Reported bruxism and biopsychosocial symptoms: a longitudinal study. *Community Dent Oral Epidemiol* **32**: 307–311.
- Anastassaki A, Magnusson T (2004). Patients referred to a specialist clinic because of suspected temporomandibular disorders: a survey of 3194 patients in respect of diagnoses, treatments, and treatment outcome. *Acta Odontol Scand* **62**: 183–192.
- Anderson GC, Gonzalez YM, Ohrbach R *et al* (2010). The research diagnostic criteria for temporomandibular disorders. VI: future directions. *J Orofac Pain* **24**: 79–88.
- Ariji Y, Sakuma S, Izumi M *et al* (2004). Ultrasonographic features of the masseter muscle in female patients with temporomandibular disorder associated with myofascial pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **98**: 337–341.
- Baba K, Haketa T, Sasaki Y, Ohya T, Clark GT (2005). Association between masseter muscle activity levels recorded during sleep and signs and symptoms of temporomandibular disorders in healthy young adults. *J Orofac Pain* **19**: 226–231.
- Bader G, Lavigne G (2000). Sleep bruxism; an overview of an oromandibular sleep movement disorder. REVIEW ARTICLE. *Sleep Med Rev* **4**: 27–43.
- Bader GG, Kampe T, Tagdae T, Karlsson S, Blomqvist M (1997). Descriptive physiological data on a sleep bruxism population. *Sleep* **20**: 982–990.

- Balasubramaniam R, de Leeuw R, Zhu H, Nickerson RB, Okeson JP, Carlson CR (2007). Prevalence of temporomandibular disorders in fibromyalgia and failed back syndrome patients: a blinded prospective comparison study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **104**: 204–216.
- Ballegaard V, Thede-Schmidt-Hansen P, Svensson P, Jensen R (2008). Are headache and temporomandibular disorders related? A blinded study. *Cephalgia* **28**: 832–841.
- Barnsley L, Lord S, Bogduk N (1994). Whiplash injury. *Pain* **58**: 283–307.
- Benoliel R, Sharav Y (2008). Masticatory myofascial pain, and tension-type and chronic daily headache. In: Sharav Y, Benoliel R, eds. *Orofacial pain and Headache*. Mosby Elsevier: Edinburgh, pp. 109–148.
- Benoliel R, Eliav E, Elishoov H, Sharav Y (1994). Diagnosis and treatment of persistent pain after trauma to the head and neck. *J Oral Maxillofac Surg* **52**: 1138–1147; discussion 1147–8.
- Benoliel R, Birman N, Eliav E, Sharav Y (2008). The International Classification of Headache Disorders: accurate diagnosis of orofacial pain? *Cephalgia* **28**: 752–762.
- Benoliel R, Eliav E, Sharav Y (2009). Self-reports of pain-related awakenings in persistent orofacial pain patients. *J Orofac Pain* **23**: 330–338.
- Benoliel R, Sela G, Teich S, Sharav Y (2011). Painful temporomandibular disorders and headaches in 359 dental and medical students. *Quintessence Int* **42**: 73–78.
- Bowley JF, Gale EN (1987). Experimental masticatory muscle pain. *J Dent Res* **66**: 1765–1769.
- Brister H, Turner JA, Aaron LA, Mancl L (2006). Self-efficacy is associated with pain, functioning, and coping in patients with chronic temporomandibular disorder pain. *J Orofac Pain* **20**: 115–124.
- Broton JG, Sessle BJ (1988). Reflex excitation of masticatory muscles induced by algescic chemicals applied to the temporomandibular joint of the cat. *Arch Oral Biol* **33**: 741–747.
- Buchner R, Van der Glas HW, Brouwers JE, Bosman F (1992). Electromyographic parameters related to clenching level and jaw-jerk reflex in patients with a simple type of myogenous cranio-mandibular disorder. *J Oral Rehabil* **19**: 495–511.
- Burgess J (1991). Symptom characteristics in TMD patients reporting blunt trauma and/or whiplash injury. *J Cranio-mandib Disord* **5**: 251–257.
- Burgess JA, Dworkin SF (1993). Litigation and post-traumatic TMD: how patients report treatment outcome. *J Am Dent Assoc* **124**: 105–110.
- Cairns BE, Hu JW, Arendt-Nielsen L, Sessle BJ, Svensson P (2001). Sex-related differences in human pain and rat afferent discharge evoked by injection of glutamate into the masseter muscle. *J Neurophysiol* **86**: 782–791.
- Cairns BE, Gambarota G, Svensson P, Arendt-Nielsen L, Berde CB (2002a). Glutamate-induced sensitization of rat masseter muscle fibers. *Neuroscience* **109**: 389–399.
- Cairns BE, Sim Y, Bereiter DA, Sessle BJ, Hu JW (2002b). Influence of sex on reflex jaw muscle activity evoked from the rat temporomandibular joint. *Brain Res* **957**: 338–344.
- Cairns BE, Svensson P, Wang K et al (2003a). Activation of peripheral NMDA receptors contributes to human pain and rat afferent discharges evoked by injection of glutamate into the masseter muscle. *J Neurophysiol* **90**: 2098–2105.
- Cairns BE, Wang K, Hu JW, Sessle BJ, Arendt-Nielsen L, Svensson P (2003b). The effect of glutamate-evoked masseter muscle pain on the human jaw-stretch reflex differs in men and women. *J Orofac Pain* **17**: 317–325.
- Campanis CM, Siqueira JT (2006). Sleep bruxism: clinical aspects and characteristics in patients with and without chronic orofacial pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **101**: 188–193.
- Campanis CM, Formigoni G, Teixeira MJ, Bittencourt LR, Tufik S, de Siqueira JT (2006). Sleep bruxism and temporomandibular disorder: clinical and polysomnographic evaluation. *Arch Oral Biol* **51**: 721–728.
- Carlson CR, Reid KI, Curran SL et al (1998). Psychological and physiological parameters of masticatory muscle pain. *Pain* **76**: 297–307.
- Carlsson GE, Egermark I, Magnusson T (2002). Predictors of signs and symptoms of temporomandibular disorders: a 20-year follow-up study from childhood to adulthood. *Acta Odontol Scand* **60**: 180–185.
- Carroll LJ, Ferrari R, Cassidy JD (2007). Reduced or painful jaw movement after collision-related injuries: a population-based study. *J Am Dent Assoc* **138**: 86–93.
- Cassidy JD, Carroll LJ, Cote P, Lemstra M, Berglund A, Nygren A (2000). Effect of eliminating compensation for pain and suffering on the outcome of insurance claims for whiplash injury. *N Engl J Med* **342**: 1179–1186.
- Chen CY, Palla S, Erni S, Sieber M, Gallo LM (2007). Nonfunctional tooth contact in healthy controls and patients with myogenous facial pain. *J Orofac Pain* **21**: 185–193.
- Choy E, Kydd WL (1988). Bite force duration: a diagnostic procedure for mandibular dysfunction. *J Prosthet Dent* **60**: 365–368.
- Christensen LV (1971). Facial pain and internal pressure of masseter muscle in experimental bruxism in man. *Arch Oral Biol* **16**: 1021–1031.
- Christensen LV (1981). Progressive jaw muscle fatigue of experimental tooth clenching in man. *J Oral Rehabil* **8**: 413–420.
- Ciancaglini R, Testa M, Radaelli G (1999). Association of neck pain with symptoms of temporomandibular dysfunction in the general adult population. *Scand J Rehabil Med* **31**: 17–22.
- Clark GT, Beemsterboer PL, Jacobson R (1984). The effect of sustained submaximal clenching on maximum bite force in myofascial pain dysfunction patients. *J Oral Rehabil* **11**: 387–391.
- Clark GT, Adler RC, Lee JJ (1991). Jaw pain and tenderness levels during and after repeated sustained maximum voluntary protrusion. *Pain* **45**: 17–22.
- Clark GT, Tsukiyama Y, Baba K, Watanabe T (1999). Sixty-eight years of experimental occlusal interference studies: what have we learned? *J Prosthet Dent* **82**: 704–713.
- Clauw DJ (2009). Fibromyalgia: an overview. *Am J Med* **122**: S3–S13.
- Cote P, Cassidy JD, Carroll L (2000). Is a lifetime history of neck injury in a traffic collision associated with prevalent neck pain, headache and depressive symptomatology? *Accid Anal Prev* **32**: 151–159.
- Dao TT, LeResche L (2000). Gender differences in pain. *J Orofac Pain* **14**: 169–184; discussion 184–95.
- Dao TT, Knight K, Ton-That V (1998). Modulation of myofascial pain by the reproductive hormones: a preliminary report. *J Prosthet Dent* **79**: 663–670.
- De Boever JA, Keersmaekers K (1996). Trauma in patients with temporomandibular disorders: frequency and treatment outcome. *J Oral Rehabil* **23**: 91–96.
- Demitrack MA, Crofford LJ (1998). Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. *Ann N Y Acad Sci* **840**: 684–697.

- Dervis E (2004). Changes in temporomandibular disorders after treatment with new complete dentures. *J Oral Rehabil* **31**: 320–326.
- Diatchenko L, Slade GD, Nackley AG et al (2005). Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* **14**: 135–143.
- Diatchenko L, Anderson AD, Slade GD et al (2006a). Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. *Am J Med Genet B Neuropsychiatr Genet* **141B**: 449–462.
- Diatchenko L, Nackley AG, Slade GD et al (2006b). Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain* **125**: 216–224.
- Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W (2006c). Idiopathic pain disorders – pathways of vulnerability. *Pain* **123**: 226–230.
- DiPaolo C, Di Nunno A, Vanacore N, Bruti G (2009). ID migraine questionnaire in temporomandibular disorders with craniofacial pain: a study by using a multidisciplinary approach. *Neurol Sci* **30**: 295–299.
- Drewes AM (1999). Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. *Rheumatology (Oxford)* **38**: 1035–1038.
- Dworkin SF, Burgess JA (1987). Orofacial pain of psychogenic origin: current concepts and classification. *J Am Dent Assoc* **115**: 565–571.
- Dworkin SF, LeResche L (1992). Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *J Craniomandib Disord* **6**: 301–355.
- Dworkin SF, Huggins KH, LeResche L et al (1990). Epidemiology of signs and symptoms in temporomandibular disorders: clinical signs in cases and controls. *J Am Dent Assoc* **120**: 273–281.
- Dworkin RH, Turk DC, Farrar JT et al (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* **113**: 9–19.
- Edwards RR, Grace E, Peterson S, Klick B, Haythornthwaite JA, Smith MT (2009). Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. *Eur J Pain* **13**: 1043–1047.
- Egermark I, Carlsson GE, Magnusson T (2001). A 20-year longitudinal study of subjective symptoms of temporomandibular disorders from childhood to adulthood. *Acta Odontol Scand* **59**: 40–48.
- Egermark I, Carlsson GE, Magnusson T (2005). A prospective long-term study of signs and symptoms of temporomandibular disorders in patients who received orthodontic treatment in childhood. *Angle Orthod* **75**: 645–650.
- Eliav E, Teich S, Nitzan D et al (2003). Facial arthralgia and myalgia: can they be differentiated by trigeminal sensory assessment? *Pain* **104**: 481–490.
- Epker J, Gatchel RJ (2000). Coping profile differences in the biopsychosocial functioning of patients with temporomandibular disorder. *Psychosom Med* **62**: 69–75.
- Epker J, Gatchel RJ, Ellis E 3rd (1999). A model for predicting chronic TMD: practical application in clinical settings. *J Am Dent Assoc* **130**: 1470–1475.
- Erdal ME, Herken H, Mutlu MN, Bayazit YA (2003). Significance of catechol-O-methyltransferase gene polymorphism in myofascial pain syndrome. *The Pain Clinic* **15**: 309–313.
- Eriksson PO, Zafar H, Haggman-Henrikson B (2004). Deranged jaw-neck motor control in whiplash-associated disorders. *Eur J Oral Sci* **112**: 25–32.
- Ernberg M, Hedenberg-Magnusson B, Alstergren P, Kopp S (1999). The level of serotonin in the superficial masseter muscle in relation to local pain and allodynia. *Life Sci* **65**: 313–325.
- Evaskus DS, Laskin DM (1972). A biochemical measure of stress in patients with myofascial pain-dysfunction syndrome. *J Dent Res* **51**: 1464–1466.
- Farella M, Bakke M, Michelotti A, Martina R (2001). Effects of prolonged gum chewing on pain and fatigue in human jaw muscles. *Eur J Oral Sci* **109**: 81–85.
- Farella M, Bakke M, Michelotti A, Rapuano A, Martina R (2003). Masseter thickness, endurance and exercise-induced pain in subjects with different vertical craniofacial morphology. *Eur J Oral Sci* **111**: 183–188.
- Ferrando M, Andreu Y, Galdon MJ, Dura E, Poveda R, Bagan JV (2004). Psychological variables and temporomandibular disorders: distress, coping, and personality. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **98**: 153–160.
- Ferrari R, Schrader H, Obelieniene D (1999). Prevalence of temporomandibular disorders associated with whiplash injury in Lithuania. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **87**: 653–657.
- Fillingim RB (2000). Sex, gender, and pain: women and men really are different. *Curr Rev Pain* **4**: 24–30.
- Fillingim RB (2002). Sex differences in analgesic responses: evidence from experimental pain models. *Eur J Anaesthesiol Suppl* **26**: 16–24.
- Fillingim RB, Ness TJ (2000). Sex-related hormonal influences on pain and analgesic responses. *Neurosci Biobehav Rev* **24**: 485–501.
- Fillingim RB, Fillingim LA, Hollins M, Sigurdsson A, Maixner W (1998). Generalized vibrotactile allodynia in a patient with temporomandibular disorder. *Pain* **78**: 75–78.
- Fischer DJ, Mueller BA, Critchlow CW, LeResche L (2006). The association of temporomandibular disorder pain with history of head and neck injury in adolescents. *J Orofac Pain* **20**: 191–198.
- Franco AL, Goncalves DA, Castanharo SM, Speciali JG, Bigal ME, Camparis CM (2010). Migraine is the most prevalent primary headache in individuals with temporomandibular disorders. *J Orofac Pain* **24**: 287–292.
- Freund B, Schwartz M (2002). Post-traumatic myofascial pain of the head and neck. *Curr Pain Headache Rep* **6**: 361–369.
- Galdon MJ, Durá E, Andreu Y, Ferrando M, Poveda R, Bagan JV (2006). Multidimensional approach to the differences between muscular and articular temporomandibular patients: Coping, distress, and pain characteristics. *Oral Surg Oral Med Oral Pathol* **102**: 40–46.
- Galli U, Gaab J, Ettlin DA, Ruggia F, Ehlert U, Palla S (2009). Enhanced negative feedback sensitivity of the hypothalamus-pituitary-adrenal axis in chronic myogenous facial pain. *Eur J Pain* **13**: 600–605.
- Garofalo JP, Gatchel RJ, Wesley AL, Ellis E 3rd (1998). Predicting chronicity in acute temporomandibular joint disorders using the research diagnostic criteria. *J Am Dent Assoc* **129**: 438–447.
- Gavish A, Winocur E, Menashe S, Halachmi M, Eli I, Gazit E (2002). Experimental chewing in myofascial pain patients. *J Orofac Pain* **16**: 22–28.
- Gay T, Maton B, Rendell J, Majourau A (1994). Characteristics of muscle fatigue in patients with myofascial pain-dysfunction syndrome. *Arch Oral Biol* **39**: 847–852.
- Ge HY, Wang K, Madeleine P, Svensson P, Sessle BJ, Arendt-Nielsen L (2004). Simultaneous modulation of the exteroceptive suppression periods in the trapezius and temporalis muscles by experimental muscle pain. *Clin Neurophysiol* **115**: 1399–1408.

- Gerwin RD, Dommerholt J, Shah JP (2004). An expansion of Simons' integrated hypothesis of trigger point formation. *Curr Pain Headache Rep* **8**: 468–475.
- Gesch D, Bernhardt O, Alte D, Kocher T, John U, Hensel E (2004a). Malocclusions and clinical signs or subjective symptoms of temporomandibular disorders (TMD) in adults. Results of the population-based Study of Health in Pomerania (SHIP). *J Orofac Orthop* **65**: 88–103.
- Gesch D, Bernhardt O, Kirbschus A (2004b). Association of malocclusion and functional occlusion with temporomandibular disorders (TMD) in adults: a systematic review of population-based studies. *Quintessence Int* **35**: 211–221.
- Gesch D, Bernhardt O, Mack F, John U, Kocher T, Alte D (2005). Association of malocclusion and functional occlusion with subjective symptoms of TMD in adults: results of the Study of Health in Pomerania (SHIP). *Angle Orthod* **75**: 183–190.
- Glaros AG, Burton E (2004). Parafunctional clenching, pain, and effort in temporomandibular disorders. *J Behav Med* **27**: 91–100.
- Glaros AG, Glass EG, Brockman D (1997). Electromyographic data from TMD patients with myofascial pain and from matched control subjects: evidence for statistical, not clinical, significance. *J Orofac Pain* **11**: 125–129.
- Glaros AG, Tabacchi KN, Glass EG (1998). Effect of parafunctional clenching on TMD pain. *J Orofac Pain* **12**: 145–152.
- Gollapudi L, Oblinger MM (1999). Estrogen and NGF synergistically protect terminally differentiated, ERalpha-transfected PC12 cells from apoptosis. *J Neurosci Res* **56**: 471–481.
- Goncalves DA, Bigal ME, Jales LC, Camparis CM, Speciali JG (2010). Headache and symptoms of temporomandibular disorder: an epidemiological study. *Headache* **50**: 231–241.
- Gracely RH, Petzke F, Wolf JM, Clauw DJ (2002). Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* **46**: 1333–1343.
- Graven-Nielsen T, Svensson P, Arendt-Nielsen L (1997). Effects of experimental muscle pain on muscle activity and co-ordination during static and dynamic motor function. *Electroencephalogr Clin Neurophysiol* **105**: 156–164.
- Greene CS, Marbach JJ (1982). Epidemiologic studies of mandibular dysfunction: a critical review. *J Prosthet Dent* **48**: 184–190.
- Gronqvist J, Haggman-Henrikson B, Eriksson PO (2008). Impaired jaw function and eating difficulties in whiplash-associated disorders. *Swed Dent J* **32**: 171–177.
- Grossi ML, Goldberg MB, Locker D, Tenenbaum HC (2008). Irritable bowel syndrome patients versus responding and nonresponding temporomandibular disorder patients: a neuropsychologic profile comparative study. *Int J Prosthodont* **21**: 201–209.
- Hagberg C, Hellsing G, Hagberg M (1990). Perception of cutaneous electrical stimulation in patients with craniomandibular disorders. *J Craniomandib Disord* **4**: 120–125.
- Haggman-Henrikson B, Zafar H, Eriksson PO (2002). Disturbed jaw behavior in whiplash-associated disorders during rhythmic jaw movements. *J Dent Res* **81**: 747–751.
- Haggman-Henrikson B, Osterlund C, Eriksson PO (2004). Endurance during chewing in whiplash-associated disorders and TMD. *J Dent Res* **83**: 946–950.
- Hatch JP, Rugh JD, Sakai S, Saunders MJ (2001). Is use of exogenous estrogen associated with temporomandibular signs and symptoms? *J Am Dent Assoc* **132**: 319–326.
- Hedenberg-Magnusson B, Ernberg M, Kopp S (1997). Symptoms and signs of temporomandibular disorders in patients with fibromyalgia and local myalgia of the temporomandibular system. A comparative study. *Acta Odontol Scand* **55**: 344–349.
- Henrikson T, Nilner M (2003). Temporomandibular disorders, occlusion and orthodontic treatment. *J Orthod* **30**: 129–137. discussion 127.
- Hirsch C (2009). No Increased risk of temporomandibular disorders and bruxism in children and adolescents during orthodontic therapy. *J Orofac Orthop* **70**: 39–50.
- Hollins M, Sigurdsson A (1998). Vibrotactile amplitude and frequency discrimination in temporomandibular disorders. *Pain* **75**: 59–67.
- How CK (2004). Orthodontic treatment has little to do with temporomandibular disorders. *Evid Based Dent* **5**: 75.
- Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT (2002). Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). *J Dent Res* **81**: 284–288.
- Inglese M, Makani S, Johnson G et al (2005). Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg* **103**: 298–303.
- Isselee H, De Laat A, De Mot B, Lysens R (2002). Pressure-pain threshold variation in temporomandibular disorder myalgia over the course of the menstrual cycle. *J Orofac Pain* **16**: 105–117.
- Jensen R, Rasmussen BK, Pedersen B, Lous I, Olesen J (1993). Prevalence of oromandibular dysfunction in a general population. *J Orofac Pain* **7**: 175–182.
- Johansson A, Unell L, Carlsson GE, Soderfeldt B, Halling A (2006). Risk factors associated with symptoms of temporomandibular disorders in a population of 50- and 60-year-old subjects. *J Oral Rehabil* **33**: 473–481.
- John MT, Miglioretti DL, LeResche L, Von Korff M, Critchlow CW (2003). Widespread pain as a risk factor for dysfunctional temporomandibular disorder pain. *Pain* **102**: 257–263.
- Karibe H, Goddard G, Gear RW (2003). Sex differences in masticatory muscle pain after chewing. *J Dent Res* **82**: 112–116.
- Kasch H, Hjorth T, Svensson P, Nyhuus L, Jensen TS (2002). Temporomandibular disorders after whiplash injury: a controlled, prospective study. *J Orofac Pain* **16**: 118–128.
- Kato T, Thie NM, Huynh N, Miyawaki S, Lavigne GJ (2003). Topical review: sleep bruxism and the role of peripheral sensory influences. *J Orofac Pain* **17**: 191–213.
- Kim MR, Graber TM, Viana MA (2002). Orthodontics and temporomandibular disorder: a meta-analysis. *Am J Orthod Dentofacial Orthop* **121**: 438–446.
- King CD, Wong F, Currie T, Mauderli AP, Fillingim RB, Riley JL 3rd (2009). Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. *Pain* **143**: 172–178.
- Klobas L, Tegelberg A, Axelsson S (2004). Symptoms and signs of temporomandibular disorders in individuals with chronic whiplash-associated disorders. *Swed Dent J* **28**: 29–36.
- Kolbinson DA, Epstein JB, Burgess JA (1996). Temporomandibular disorders, headaches, and neck pain following motor vehicle accidents and the effect of litigation: review of the literature. *J Orofac Pain* **10**: 101–125.
- Kolbinson DA, Epstein JB, Burgess JA, Senthilselvan A (1997a). Temporomandibular disorders, headaches, and neck pain after motor vehicle accidents: a pilot investigation of persistence and litigation effects. *J Prosthet Dent* **77**: 46–53.

- Kolbinson DA, Epstein JB, Senthilselvan A, Burgess JA (1997b). A comparison of TMD patients with or without prior motor vehicle accident involvement: initial signs, symptoms, and diagnostic characteristics. *J Orofac Pain* **11**: 206–214.
- Kopp S (2001). Neuroendocrine, immune, and local responses related to temporomandibular disorders. *J Orofac Pain* **15**: 9–28.
- Korszun A, Papadopoulos E, Demitrack M, Engleberg C, Crofford L (1998). The relationship between temporomandibular disorders and stress-associated syndromes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **86**: 416–420.
- Lasch KE (2002). Culture and Pain. *Pain, Clinical Updates X*: Available at: <http://www.iasp-pain.org>.
- Lavigne GJ, Velly-Miguel AM, Montplaisir J (1991). Muscle pain, dyskinesia, and sleep. *Can J Physiol Pharmacol* **69**: 678–682.
- Lavigne GJ, Rompre PH, Montplaisir JY (1996). Sleep bruxism: validity of clinical research diagnostic criteria in a controlled polysomnographic study. *J Dent Res* **75**: 546–552.
- Lavigne GJ, Rompre PH, Poirier G, Huard H, Kato T, Montplaisir JY (2001). Rhythmic masticatory muscle activity during sleep in humans. *J Dent Res* **80**: 443–448.
- Le Bell Y, Niemi PM, Jamsa T, Kylmala M, Alanen P (2006). Subjective reactions to intervention with artificial interferences in subjects with and without a history of temporomandibular disorders. *Acta Odontol Scand* **64**: 59–63.
- Lee JS, Ro JY (2007). Peripheral metabotropic glutamate receptor 5 mediates mechanical hypersensitivity in craniofacial muscle via protein kinase C dependent mechanisms. *Neuroscience* **146**: 375–383.
- de Leeuw R (2008). *Orofacial pain: guidelines for assessment, classification, and management*. The American Academy of Orofacial Pain, 4th edn. Quintessence Publishing Co., Inc.: Chicago.
- LeResche L (1997). Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. *Crit Rev Oral Biol Med* **8**: 291–305.
- LeResche L, Dworkin SF, Sommers EE, Truelove EL (1991). An epidemiologic evaluation of two diagnostic classification schemes for temporomandibular disorders. *J Prosthet Dent* **65**: 131–137.
- LeResche L, Saunders K, Von Korff MR, Barlow W, Dworkin SF (1997). Use of exogenous hormones and risk of temporomandibular disorder pain. *Pain* **69**: 153–160.
- LeResche L, Mancl L, Sherman JJ, Gandara B, Dworkin SF (2003). Changes in temporomandibular pain and other symptoms across the menstrual cycle. *Pain* **106**: 253–261.
- LeResche L, Mancl LA, Drangsholt MT, Saunders K, Korff MV (2005a). Relationship of pain and symptoms to pubertal development in adolescents. *Pain* **118**: 201–209.
- LeResche L, Sherman JJ, Huggins K et al (2005b). Musculoskeletal orofacial pain and other signs and symptoms of temporomandibular disorders during pregnancy: a prospective study. *J Orofac Pain* **19**: 193–201.
- Levitt SR, McKinney MW (1994). Validating the TMJ scale in a national sample of 10,000 patients: demographic and epidemiologic characteristics. *J Orofac Pain* **8**: 25–35.
- Light KC, Bragdon EE, Grewen KM, Brownley KA, Girdler SS, Maixner W (2009). Adrenergic dysregulation and pain with and without acute beta-blockade in women with fibromyalgia and temporomandibular disorder. *J Pain* **10**: 542–552.
- Lindroth JE, Schmidt JE, Carlson CR (2002). A comparison between masticatory muscle pain patients and intracapsular pain patients on behavioral and psychosocial domains. *J Orofac Pain* **16**: 277–283.
- List T, Wahlund K, Wenneberg B, Dworkin SF (1999). TMD in children and adolescents: prevalence of pain, gender differences, and perceived treatment need. *J Orofac Pain* **13**: 9–20.
- Lobbezoo F, Lavigne GJ (1997). Do bruxism and temporomandibular disorders have a cause-and-effect relationship? *J Orofac Pain* **11**: 15–23.
- Lobbezoo F, Drangsholt M, Peck C, Sato H, Kopp S, Svensson P (2004). Topical review: new insights into the pathology and diagnosis of disorders of the temporomandibular joint. *J Orofac Pain* **18**: 181–191.
- Lobbezoo F, van Selms MK, Naeije M (2006). Masticatory muscle pain and disordered jaw motor behaviour: literature review over the past decade. *Arch Oral Biol* **51**: 713–720.
- Look JO, John MT, Tai F et al (2010). The Research Diagnostic Criteria For Temporomandibular Disorders. II: reliability of Axis I diagnoses and selected clinical measures. *J Orofac Pain* **24**: 25–34.
- Lund JP, Stohler CS (1994). Effects of pain on muscular activity in temporomandibular disorders and related conditions. In: Stohler CS, Carlson DS, eds *Biological and psychological aspects of orofacial pain*. University of Michigan: Ann Arbor, pp. 74–91.
- Lund JP, Donga R, Widmer CG, Stohler CS (1991). The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol* **69**: 683–694.
- Luther F, Layton S, McDonald F (2010). Orthodontics for treating temporomandibular joint (TMJ) disorders. *Cochrane Database Syst Rev*. Issue 7. Art. No.: CD006541. DOI: 10.1002/14651858. CD006541.pub2.
- Macfarlane TV, Gray RJM, Kincey J, Worthington HV (2001). Factors associated with the temporomandibular disorder, pain dysfunction syndrome (PDS): Manchester case-control study. *Oral Dis* **7**: 321–330.
- Macfarlane TV, Blinkhorn AS, Davies RM, Kincey J, Worthington HV (2003a). Factors associated with health care seeking behaviour for orofacial pain in the general population. *Community Dent Health* **20**: 20–26.
- Macfarlane TV, Blinkhorn AS, Davies RM, Worthington HV (2003b). Association between local mechanical factors and orofacial pain: survey in the community. *J Dent* **31**: 535–542.
- Macfarlane TV, Kenealy P, Kingdon HA et al (2009). Twenty-year cohort study of health gain from orthodontic treatment: temporomandibular disorders. *Am J Orthod Dentofacial Orthop* **135**: 692. 1–8. discussion 692–3..
- Maekawa K, Clark GT, Kuboki T (2002). Intramuscular hypoperfusion, adrenergic receptors, and chronic muscle pain. *J Pain* **3**: 251–260.
- Magnusson T, Egermark I, Carlsson GE (2000). A longitudinal epidemiologic study of signs and symptoms of temporomandibular disorders from 15 to 35 years of age. *J Orofac Pain* **14**: 310–319.
- Magnusson T, Egermark I, Carlsson GE (2005). A prospective investigation over two decades on signs and symptoms of temporomandibular disorders and associated variables. A final summary. *Acta Odontol Scand* **63**: 99–109.
- Maixner W, Fillingim R, Booker D, Sigurdsson A (1995). Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. *Pain* **63**: 341–351.
- Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S (1998). Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. *Pain* **76**: 71–81.
- Mann MK, Dong XD, Svensson P, Cairns BE (2006). Influence of intramuscular nerve growth factor injection on the response properties of rat masseter muscle afferent fibers. *J Orofac Pain* **20**: 325–336.

- Marbach JJ, Levitt M (1976). Erythrocyte catechol-O-methyltransferase activity in facial pain patients. *J Dent Res* **55**: 711.
- Marbach JJ, Raphael KG, Dohrenwend BP, Lennon MC (1990). The validity of tooth grinding measures: etiology of pain dysfunction syndrome revisited. *J Am Dent Assoc* **120**: 327–333.
- Marbach JJ, Raphael KG, Janal MN, Hirschhorn-Roth R (2003). Reliability of clinician judgements of bruxism. *J Oral Rehabil* **30**: 113–118.
- Martinez-Lavin M (2004). Fibromyalgia as a sympathetically maintained pain syndrome. *Curr Pain Headache Rep* **8**: 385–389.
- McNamara JA Jr (1997). Orthodontic treatment and temporomandibular disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **83**: 107–117.
- McNamara JA Jr, Seligman DA, Okeson JP (1995). Occlusion, Orthodontic treatment, and temporomandibular disorders: a review. *J Orofac Pain* **9**: 73–90.
- Melis M, Lobo SL, Ceneviz C et al (2010). Effect of cigarette smoking on pain intensity of TMD patients: a pilot study. *Cranio* **28**: 187–192.
- Mense S (2002). Do we know enough to put forward a unifying hypothesis? *J Pain* **3**: 264–267. discussion 270–1.
- Mense S (2003). The pathogenesis of muscle pain. *Curr Pain Headache Rep* **7**: 419–425.
- van der Meulen MJ, Lobbezoo F, Aartman IH, Naeije M (2006). Self-reported oral parafunctions and pain intensity in temporomandibular disorder patients. *J Orofac Pain* **20**: 31–35.
- Michalowicz BS, Pihlstrom BL, Hodges JS, Bouchard TJ Jr (2000). No heritability of temporomandibular joint signs and symptoms. *J Dent Res* **79**: 1573–1578.
- Michelotti A, Iodice G (2010). The role of orthodontics in temporomandibular disorders. *J Oral Rehabil* **37**: 411–429.
- Mohlin BO, Derweduwen K, Pilley R, Kingdon A, Shaw WC, Kenealy P (2004). Malocclusion and temporomandibular disorder: a comparison of adolescents with moderate to severe dysfunction with those without signs and symptoms of temporomandibular disorder and their further development to 30 years of age. *Angle Orthod* **74**: 319–327.
- Morris DB (2001). Ethnicity and Pain. *Pain, Clinical Updates* **IX**: Available at: <http://www.iasp-pain.org>.
- Murray GM, Peck CC (2007). Orofacial pain and jaw muscle activity: a new model. *J Orofac Pain* **21**: 263–278. discussion 279–88.
- Nackley AG, Tan KS, Fecho K, Flood P, Diatchenko L, Maixner W (2007). Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors. *Pain* **128**: 199–208.
- Ng B, Dimsdale JE, Rollnik JD, Shapiro H (1996). The effect of ethnicity on prescriptions for patient-controlled analgesia for post-operative pain. *Pain* **66**: 9–12.
- Ohayon MM (2005). Relationship between chronic painful physical condition and insomnia. *J Psychiatr Res* **39**: 151–159.
- Ohrbach R, Turner JA, Sherman JJ et al (2010). The Research Diagnostic Criteria for Temporomandibular Disorders. IV: evaluation of psychometric properties of the Axis II measures. *J Orofac Pain* **24**: 48–62.
- Ojima K, Watanabe N, Narita N, Narita M (2007). Temporomandibular disorder is associated with a serotonin transporter gene polymorphism in the Japanese population. *Biopsychosoc Med* **1**: 3.
- Okeson JP (1996). *Orofacial pain: guidelines for assessment, classification, and management*. The American Academy of Orofacial Pain. Quintessence Publishing Co., Inc.: Illinois, USA.
- Olesen J, Bousser M-G, Diener HC et al (2004). The International Classification of Headache Disorders, 2nd Edition. *Cephalalgia* **24** (Suppl 1): 24–150.
- Osterberg T, Carlsson GE, Wedel A, Johansson U (1992). A cross-sectional and longitudinal study of craniomandibular dysfunction in an elderly population. *J Craniomandib Disord* **6**: 237–245.
- Pahkala R, Qvarnstrom M (2004). Can temporomandibular dysfunction signs be predicted by early morphological or functional variables? *Eur J Orthod* **26**: 367–373.
- Perez del Palomar A, Doblare M (2008). Dynamic 3D FE modelling of the human temporomandibular joint during whiplash. *Med Eng Phys* **30**: 700–709.
- Pergamalian A, Rudy TE, Zaki HS, Greco CM (2003). The association between wear facets, bruxism, and severity of facial pain in patients with temporomandibular disorders. *J Prosthet Dent* **90**: 194–200.
- Petty BG, Cornblath DR, Adornato BT et al (1994). The effect of systemically administered recombinant human nerve growth factor in healthy human subjects. *Ann Neurol* **36**: 244–246.
- Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M (2009). Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and Fibromyalgia Syndrome. *Pain* **147**: 72–83.
- Phillips JM, Gatchel RJ, Wesley AL, Ellis E 3rd (2001). Clinical implications of sex in acute temporomandibular disorders. *J Am Dent Assoc* **132**: 49–57.
- Plesh O, Gansky SA, Curtis DA, Pogrel MA (1999). The relationship between chronic facial pain and a history of trauma and surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **88**: 16–21.
- Povlishock JT, Katz DI (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *J Head Trauma Rehabil* **20**: 76–94.
- Pullinger AG, Seligman DA (1991). Trauma history in diagnostic groups of temporomandibular disorders. *Oral Surg Oral Med Oral Pathol* **71**: 529–534.
- Puri V, Cui L, Liverman CS et al (2005). Ovarian steroids regulate neuropeptides in the trigeminal ganglion. *Neuropeptides* **39**: 409–417.
- Raphael KG, Marbach JJ, Gallagher RM, Dohrenwend BP (1999). Myofascial TMD does not run in families. *Pain* **80**: 15–22.
- Raphael KG, Marbach JJ, Gallagher RM (2000). Somatosensory amplification and affective inhibition are elevated in myofascial face pain. *Pain Med* **1**: 247–253.
- Raphael KG, Janal MN, Anathan S, Cook DB, Staud R (2009). Temporal summation of heat pain in temporomandibular disorder patients. *J Orofac Pain* **23**: 54–64.
- Reid KI, Carlson CR, Sherman JJ, Curran SL, Gracely RH (1996). Influence of a sympathomimetic amine on masticatory and trapezius pain/pressure thresholds and electromyographic levels. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **82**: 525–531.
- Reiter S, Eli I, Gavish A, Winocur E (2006). Ethnic differences in temporomandibular disorders between Jewish and Arab populations in Israel according to RDC/TMD evaluation. *J Orofac Pain* **20**: 36–42.
- Riley JL 3rd, Robinson ME, Wise EA, Myers CD, Fillingim RB (1998). Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain* **74**: 181–187.
- Riley JL 3rd, Robinson ME, Wise EA, Price DD (1999). A meta-analytic review of pain perception across the menstrual cycle. *Pain* **81**: 225–235.

- Riley JL 3rd, Benson MB, Gremillion HA *et al* (2001). Sleep disturbance in orofacial pain patients: pain-related or emotional distress? *Cranio* **19**: 106–113.
- Ro JY, Capra NF, Masri R (2004). Contribution of peripheral N-methyl-D-aspartate receptors to c-fos expression in the trigeminal spinal nucleus following acute masseteric inflammation. *Neuroscience* **123**: 213–219.
- Rompere PH, Daigle-Landry D, Guitard F, Montplaisir JY, Lavigne GJ (2007). Identification of a sleep bruxism subgroup with a higher risk of pain. *J Dent Res* **86**: 837–842.
- Rugh JD, Barghi N, Drago CJ (1984). Experimental occlusal discrepancies and nocturnal bruxism. *J Prosthet Dent* **51**: 548–553.
- Sale H, Hedman L, Isberg A (2010). Accuracy of patients' recall of temporomandibular joint pain and dysfunction after experiencing whiplash trauma: a prospective study. *J Am Dent Assoc* **141**: 879–886.
- Sarlani E, Grace EG, Reynolds MA, Greenspan JD (2004). Evidence for up-regulated central nociceptive processing in patients with masticatory myofascial pain. *J Orofac Pain* **18**: 41–55.
- Sarzi-Putini P, Atzeni F, Diana A, Doria A, Furlan R (2006). Increased neural sympathetic activation in fibromyalgia syndrome. *Ann N Y Acad Sci* **1069**: 109–117.
- Schiffman EL, Friction JR, Haley DP, Shapiro BL (1990). The prevalence and treatment needs of subjects with temporomandibular disorders. *J Am Dent Assoc* **120**: 295–303.
- Schiffman EL, Anderson GC, Friction JR, Lindgren BR (1992). The relationship between level of mandibular pain and dysfunction and stage of temporomandibular joint internal derangement. *J Dent Res* **71**: 1812–1815.
- Schiffman EL, Ohrbach R, Truelove EL *et al* (2010a). The Research Diagnostic Criteria for Temporomandibular Disorders. V: methods used to establish and validate revised Axis I diagnostic algorithms. *J Orofac Pain* **24**: 63–78.
- Schiffman EL, Truelove EL, Ohrbach R *et al* (2010b). The Research Diagnostic Criteria for Temporomandibular Disorders. I: overview and methodology for assessment of validity. *J Orofac Pain* **24**: 7–24.
- Schmidt-Hansen PT, Svensson P, Jensen TS, Graven-Nielsen T, Bach FW (2006). Patterns of experimentally induced pain in pericranial muscles. *Cephalalgia* **26**: 568–577.
- Schnurr RF, Rollman GB, Brooke RI (1991). Are there psychologic predictors of treatment outcome in temporomandibular joint pain and dysfunction? *Oral Surg Oral Med Oral Pathol* **72**: 550–558.
- Schutz TC, Andersen ML, Tufik S (2009). The influence of orofacial pain on sleep pattern: a review of theory, animal models and future directions. *Sleep Med* **10**: 822–828.
- Scott DS, Lundeen TF (1980). Myofascial pain involving the masticatory muscles: an experimental model. *Pain* **8**: 207–215.
- Selaimen CM, Jeronimo JC, Brilhante DP, Grossi ML (2006). Sleep and depression as risk indicators for temporomandibular disorders in a cross-cultural perspective: a case-control study. *Int J Prosthodont* **19**: 154–161.
- Sessle BJ (1999). The neural basis of temporomandibular joint and masticatory muscle pain. *J Orofac Pain* **13**: 238–245.
- Sessle BJ, Hu JW (1991). Mechanisms of pain arising from articular tissues. *Can J Physiol Pharmacol* **69**: 617–626.
- Shah JP, Phillips TM, Danoff JV, Gerber LH (2005). An *in vivo* microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. *J Appl Physiol* **99**: 1977–1984.
- Sheiner EK, Sheiner E, Shoham-Vardi I, Mazor M, Katz M (1999). Ethnic differences influence care giver's estimates of pain during labour. *Pain* **81**: 299–305.
- Sherman JJ, LeResche L, Huggins KH, Mancil LA, Sage JC, Dworkin SF (2004). The relationship of somatization and depression to experimental pain response in women with temporomandibular disorders. *Psychosom Med* **66**: 852–860.
- Shiau YY, Peng CC, Wen SC, Lin LD, Wang JS, Lou KL (2003). The effects of masseter muscle pain on biting performance. *J Oral Rehabil* **30**: 978–984.
- Simons DG (2004). Review of enigmatic MTrPs as a common cause of enigmatic musculoskeletal pain and dysfunction. *J Electromyogr Kinesiol* **14**: 95–107.
- Smith MT, Haythornthwaite JA (2004). How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev* **8**: 119–132.
- Smith MT, Edwards RR, McCann UD, Haythornthwaite JA (2007). The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* **30**: 494–505.
- Smith MT, Wickwire EM, Grace EG *et al* (2009). Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder. *Sleep* **32**: 779–790.
- Solberg WK, Woo MW, Houston JB (1979). Prevalence of mandibular dysfunction in young adults. *J Am Dent Assoc* **98**: 25–34.
- Solomon S (2005). Chronic post-traumatic neck and head pain. *Headache* **45**: 53–67.
- Sonnenes L, Svensson P (2008). Temporomandibular disorders and psychological status in adult patients with a deep bite. *Eur J Orthod* **30**: 621–629.
- Spitzer WO, Skovron ML, Salmi LR *et al* (1995). Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. *Spine* **20**: 1S–73S.
- Steed PA, Wexler GB (2001). Temporomandibular disorders – traumatic etiology vs. nontraumatic etiology: a clinical and methodological inquiry into symptomatology and treatment outcomes. *Cranio* **19**: 188–194.
- Stohler CS, Kowalski CJ, Lund JP (2001). Muscle pain inhibits cutaneous touch perception. *Pain* **92**: 327–333.
- Stuginski-Barbosa J, Macedo HR, Bigal ME, Speciali JG (2010). Signs of temporomandibular disorders in migraine patients: a prospective, controlled study. *Clin J Pain* **26**: 418–421.
- Suvinen TI, Reade PC, Kemppainen P, Kononen M, Dworkin SF (2005). Review of aetiological concepts of temporomandibular pain disorders: towards a biopsychosocial model for integration of physical disorder factors with psychological and psychosocial illness impact factors. *Eur J Pain* **9**: 613–633.
- Svensson P, Graven-Nielsen T (2001). Craniofacial muscle pain: review of mechanisms and clinical manifestations. *J Orofac Pain* **15**: 117–145.
- Svensson P, Arendt-Nielsen L, Houe L (1998a). Muscle pain modulates mastication: an experimental study in humans. *J Orofac Pain* **12**: 7–16.
- Svensson P, Graven-Nielsen T, Arendt-Nielsen L (1998b). Mechanical hyperesthesia of human facial skin induced by tonic painful stimulation of jaw muscles. *Pain* **74**: 93–100.
- Svensson P, List T, Hector G (2001). Analysis of stimulus-evoked pain in patients with myofascial temporomandibular pain disorders. *Pain* **92**: 399–409.
- Svensson P, Cairns BE, Wang K, Arendt-Nielsen L (2003). Injection of nerve growth factor into human masseter muscle evokes long-lasting mechanical allodynia and hyperalgesia. *Pain* **104**: 241–247.
- Svensson P, Castrillon E, Cairns BE (2008a). Nerve growth factor-evoked masseter muscle sensitization and perturbation of jaw motor function in healthy women. *J Orofac Pain* **22**: 340–348.

- Svensson P, Jadidi F, Arima T, Baad-Hansen L, Sessle BJ (2008b). Relationships between craniofacial pain and bruxism. *J Oral Rehabil* **35**: 524–547.
- Svensson P, Wang K, Arendt-Nielsen L, Cairns BE (2008c). Effects of NGF-induced muscle sensitization on proprioception and nociception. *Exp Brain Res* **189**: 1–10.
- Svensson P, Wang MW, Dong XD, Kumar U, Cairns BE (2010). Human nerve growth factor sensitizes masseter muscle nociceptors in female rats. *Pain* **148**: 473–480.
- Tallents RH, Catania J, Sommers E (1991). Temporomandibular joint findings in pediatric populations and young adults: a critical review. *Angle Orthod* **61**: 7–16.
- Tchivileva IE, Lim PF, Smith SB et al (2010). Effect of catechol-O-methyltransferase polymorphism on response to propranolol therapy in chronic musculoskeletal pain: a randomized, double-blind, placebo-controlled, crossover pilot study. *Pharmacogenet Genomics* **20**: 239–248.
- Thilander B, Rubio G, Pena L, de Mayorga C (2002). Prevalence of temporomandibular dysfunction and its association with malocclusion in children and adolescents: an epidemiologic study related to specified stages of dental development. *Angle Orthod* **72**: 146–154.
- Truelove E, Pan W, Look JO et al (2010). The Research Diagnostic Criteria for Temporomandibular Disorders. III: validity of Axis I diagnoses. *J Orofac Pain* **24**: 35–47.
- Turp JC, Kowalski CJ, Stohler CS (1997). Temporomandibular disorders – pain outside the head and face is rarely acknowledged in the chief complaint. *J Prosthet Dent* **78**: 592–595.
- Turp JC, Kowalski CJ, O’Leary N, Stohler CS (1998). Pain maps from facial pain patients indicate a broad pain geography. *J Dent Res* **77**: 1465–1472.
- Turp JC, Schindler HJ, Pritsch M, Rong Q (2002). Antero-posterior activity changes in the superficial masseter muscle after exposure to experimental pain. *Eur J Oral Sci* **110**: 83–91.
- Vazquez-Delgado E, Schmidt J, Carlson C, DeLeeuw R, Okeson J (2004). Psychological and sleep quality differences between chronic daily headache and temporomandibular disorders patients. *Cephalalgia* **24**: 446–454.
- Velly AM, Gornitsky M, Philippe P (2003). Contributing factors to chronic myofascial pain: a case-control study. *Pain* **104**: 491–499.
- Velly AM, Look JO, Schiffman E et al (2010). The effect of fibromyalgia and widespread pain on the clinically significant temporomandibular muscle and joint pain disorders—a prospective 18-month cohort study. *J Pain* **11**: 1155–1164.
- Vgontzas AN, Chrousos GP (2002). Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinol Metab Clin North Am* **31**: 15–36.
- Vierck CJ Jr (2006). Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain* **124**: 242–263.
- Visscher C, Hofman N, Mes C, Lousberg R, Naeije M (2005). Is temporomandibular pain in chronic whiplash-associated disorders part of a more widespread pain syndrome? *Clin J Pain* **21**: 353–357.
- Wang K, Svensson P, Sessle BJ, Cairns BE, Arendt-Nielsen L (2010). Interactions of glutamate and capsaicin-evoked muscle pain on jaw motor functions of men. *Clin Neurophysiol* **121**: 950–956.
- Weingarten TN, Iverson BC, Shi Y, Schroeder DR, Warner DO, Reid KI (2009). Impact of tobacco use on the symptoms of painful temporomandibular joint disorders. *Pain* **147**: 67–71.
- White BA, Williams LA, Leben JR (2001). Health care utilization and cost among health maintenance organization members with temporomandibular disorders. *J Orofac Pain* **15**: 158–169.
- Winocur E, Gavish A, Voikovitch M, Emodi-Perlman A, Eli I (2003). Drugs and bruxism: a critical review. *J Orofac Pain* **17**: 99–111.
- Woda A, Pionchon P (1999). A unified concept of idiopathic orofacial pain: clinical features. *J Orofac Pain* **13**: 172–184. discussion 185–95.
- Wolfe F, Smythe HA, Yunus MB et al (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* **33**: 160–172.
- Wong MC, McMillan AS, Zheng J, Lam CL (2008). The consequences of orofacial pain symptoms: a population-based study in Hong Kong. *Community Dent Oral Epidemiol* **36**: 417–424.
- Yap AU, Dworkin SF, Chua EK, List T, Tan KB, Tan HH (2003). Prevalence of temporomandibular disorder subtypes, psychologic distress, and psychosocial dysfunction in Asian patients. *J Orofac Pain* **17**: 21–28.
- Yatani H, Studts J, Cordova M, Carlson CR, Okeson JP (2002). Comparison of sleep quality and clinical and psychologic characteristics in patients with temporomandibular disorders. *J Orofac Pain* **16**: 221–228.
- Zubieta JK, Heitzeg MM, Smith YR et al (2003). COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* **299**: 1240–1243.