Masticatory Muscle Pain and Disorders

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Abstract
This chapter represents a concerted attempt to provide the clinician with a comprehensive overview on the basic neurobiological mechanisms underlying the many different manifestations of jaw muscle pain. The range of conditions varies from muscle pain being secondary to other diseases and conditions to being the primary pain condition, i.e., there are no obvious causes or known etiological factors for the pain or dysfunction. A careful history and clinical examination of the jaw and neck muscles will facilitate a tentative diagnosis which may be followed by the need for additional examinations and investigations. This chapter will aid in the diagnostic process and institution of appropriate therapy for masticatory muscle pain.

Introduction

Muscular pain or myalgia is a common experience in daily life. Functional limitations related to muscular pain are also common and may significantly reduce quality of life. For example, back pain can reduce working ability, while pain in the legs can make running impossible and impede normal mobility. Muscular pain in the orofacial region can limit important jaw functions such as chewing and yawning and can moreover lead to perceived changes in tooth contacts due to altered sensorimotor function.

Muscular pain is categorized as a deep somatic pain that is usually constant, dull and aching, and may be accompanied by occasional exacerbations of sharp pain. Jaw muscle pain is typically difficult to localize and can be referred to and perceived in other areas, such as in the teeth, temporomandibular joints, ear, temple and eyes (Wright 2000). Of interest, myalgia is the most common non-dental pain in the orofacial region. Once an odontogenic origin for the orofacial pain complaint has been excluded, the next step is to eliminate the musculoskeletal system as a possible source of pain.

Muscular pain can be classified topographically as: 1) focal masticatory myalgia, 2) regional craniocervical myalgia involving jaw and neck muscles on the same side and 3) widespread myalgia, in which chronic musculoskeletal pain involves masticatory muscles too (Clark 2008). For focal and regional myalgia, characterized by the patient's report of pain and tenderness and localized pain on palpation, the term "myofascial pain" (MP) is commonly used. In the past, this term was associated to a specific pathophysiological condition characterized by taut bands, trigger

points (TrPs) (hyperirritable spots in the fascia surrounding skeletal muscle) within the taut band and referred pain upon sustained compression of the TrPs. For widespread chronic musculoskeletal pain, if the appropriate criteria are satisfied, then the term "fibromyalgia" (FM) is used (Wolfe et al. 2010). Fibromyalgia is a syndrome of chronic widespread pain typically accompanied by fatigue, non-restorative sleep, cognitive dysfunction, and mood disorders.

Temporomandibular disorders (TMDs) are a significant orofacial pain complaint since they represent a health problem that affects between 5 to 12% of the general population. TMDs of muscle origin are the most frequently diagnosed conditions in the community (Lobbezoo et al. 2004). In this patient population, the putative mechanisms behind masticatory muscle pain typically include overuse of a normally perfused muscle or ischemia of a normally working muscle, sympathetic reflexes that produce changes in vascular supply and muscle tone, and changes in psychological and emotional states. However, the specific risk factors, etiology and pathophysiology remain an ongoing area for research with the majority of evidence pointing towards a complex and multifactorial interaction (Svensson and Kumar 2016). There are also other less frequent disorders with associated muscular pain and functional disability in the orofacial region such as movement disorders and others.

Neurophysiology of Masticatory Muscle Pain

The mechanisms that underlie pain in skeletal muscles are still not well understood. Acute muscle pain is caused by the activation of nociceptors: these receptors are specialized for the detection of stimuli that are potentially damaging to tissue and that may lead to the perception of pain. They consist of free nerve endings and are connected to the central nervous system (CNS) by way of unmyelinated (group IV) or thinly myelinated (group III) fibers. They can be activated and sensitized by high-intensity mechanical stimuli, such as trauma or mechanical overloading, as well as by endogenous inflammatory mediators including bradykinin (BK), serotonin, and prostaglandin E2 (PGE2) (Mense 2008). A nociceptor will become activated when the nociceptive terminal is sufficiently depolarized from the normal resting membrane potential of the nerve. This depolarization is determined by a flow of positive ions (Na+) through the neural membrane, owing to receptors of channel proteins that span the membrane of the neural ending. Adenosine

triphosphate (ATP) and protons (H+) are particularly important for the generation of muscle pain. These chemical substances activate nerve endings by binding to specific receptors located in the membrane of the nerve ending. H+ plays a role in acute physiologic pain, when H+ are released due to lowered pH secondary to ischemia. A drop in pH is probably one of the main activators of peripheral nociceptors, as many painful muscle disorders (eg local myalgia, myospasm, myositis) are speculated to be associated with low pH in muscle tissue. H+ activates muscle nociceptors binding acid-sensing ion channels (ASICs) and transient receptor potential vanilloid 1 (TRPV1). ATP also seems to play a determinant role in inflammatory muscle pain (eg myositis). ATP released by lysed cells following mild tissue damage from exhaustive muscle function, activates muscle nociceptors mainly binding P2X3 receptor, a purinergic molecule.

It has been suggested (Weinkauf et al. 2015) that nerve growth factor (NGF) also plays a role in inflammatory muscle pain. The signaling of NGF in the nociceptor neurons is mediated through the high-affinity tropomyosin-related kinase A (TrkA). NGF signaling through TrkA activates the cellular protein kinases which leads to the phosphorylation and activation of TRPV1 for increased channel activity (Kumar and Mahal 2012). Furthermore, NGF causes low-frequency firing of action potentials from neural endings that may only lead to subthreshold excitatory postsynaptic potentials (EPSPs) not activating the second order neuron and thus not resulting in conscious pain, but nonetheless can sensitize the second order neuron and predispose to chronic pain (Murray and Peck 2010). This mechanism may explain, from a clinical point of view why repetitive muscular activity such as awake clenching or sleep bruxism could lead to microtrauma within the muscle which, because of NGF release, elicits low-frequency firing in muscular nociceptors without reaching pain sensation consciousness. Nonetheless, low-frequency firing may sensitize second order neurons in the subnucleus caudalis, and predispose to a chronic muscular pain condition (Murray and Peck 2010) (Figure 1).

Chemical mediators long associated with nociceptive transmission and CNS modulation, such as glutamate and gamma aminobutyric acid (GABA), have been shown to act peripherally to influence the excitability of nociceptors (Sessle 2006). Glutamate can be released by peripheral nerve ending afferents and both experimental animal and human studies have demonstrated that it is able to elicit a nociceptive response by activating excitatory amino acid receptors (N-methyl-D-aspartate (NMDA)) located on the afferent endings (Cairns et al. 2001; Svensson et al 2003; Castrillon et al. 2012). The result of this increased peripheral activity with release of neuroactive substances results

in sensitization of nociceptive endings (peripheral sensitization). Consequently, nociceptors are more likely to fire action potentials because of increased neuronal excitability. The neurobiological phenomenon of peripheral sensitization may help to explain why, in some muscular pain patients, normal muscular contractions, muscle stretch, and even muscles at rest can become painful. Furthermore, nociceptors that are normally silent become activated. In addition, this peripheral activity can lead to the release of other neuroactive substances such as Substance P and calcitonin-gene-related-peptide (CGRP) which will induce local edema by dilating the local blood vessels and increasing their permeability. Thus, a nociceptor can alter the microcirculation in its immediate neighborhood by releasing neuropeptides (Mense 2008).

Peripheral sensitization can also explain allodynia and hyperalgesia frequently observed in patients with muscle pain as increased tenderness and pain to palpation. Allodynia refers to a pain sensation following a non-noxious stimulus, such as pain on muscular palpation or muscular pain during normal function. Hyperalgesia refers to an increased sensation of pain with respect to what normally is expected after the exposure to a noxious stimulus.

Once the nociceptive signal is generated, it propagates toward its first synapse with the second-order neurons in the subnucleus caudalis as well as subnucleus oralis and subnecleus interpolaris where action potentials are generated sending the nociceptive information further on to higher CNS centers.

The small-diameter primary afferents innervating masticatory muscles have their cell bodies in the trigeminal ganglion and project to the brainstem, where they terminate in the trigeminal brainstem sensory nuclear complex (VBSNC). Here they release excitatory neurochemicals such as excitatory amino acids (eg glutamate) and neuropeptides (eg substance P) that are involved in the activation of the second order neurons in the VBSNC (Sessle 2006). Nociceptive primary afferents from masticatory muscles terminate mainly in the subnucleus caudalis of the VBSNC which is the principal brainstem relay site of trigeminal nociceptive information (Woda 2003).

There are three subtypes of second order neurons within the subnucleus caudalis: 1) low-threshold mechanoreceptive (LTM) neurons (activated by light tactile stimuli), 2) nociceptive specific (NS) neurons (respond only to noxious stimuli), 3) wide dynamic range (WDR) neurons (respond to both non-noxious and noxious stimuli). The vast majority of NS and WDR neurons have a superficial receptive field thus responding to cutaneous and mucosal tissues stimuli. However most of these neurons can be activated by other afferent inputs from deep tissues, such as masticatory muscles,

temporomandibular joints (TMJs) or tooth pulps. Due to the possible convergence of sensory information from different tissues on the second order neurons, it is quite difficult at cortical levels to identify the specific location of the noxious stimulus. In addition to central sensitization processes and impacts from descending pain modulatory pathways, this may be part of the reason why patients with muscular pain may experience referral of pain and poor localization of their pain. Many of the nociceptive neurons also receive afferent inputs from other cranial nerves or cervical nerves. These convergences have indeed been implicated in pain spread and referred pain. Furthermore, evidence consistent with the hypothesis that central neural mechanisms that integrate nociceptive inputs from deep craniofacial tissues are different in males and females has been reported (Bereiter et al. 2011). It should also be noted that referred muscle pain most likely involve cortical mechanisms to explain "mis-localization". Experimental studies have shown that individuals with referred pain localized to the wrist following local painful stimulation of the forearm muscles in fact demonstrate activation of the somatotopic appropriate location of the primary somatosensory cortex, i.e., the wrist area seems to be activated even in the absence of a nociceptive input from that area (Macefield et al. 2007). This would indicate that referred pain is akin to "virtual" pain in the brain. Two main mechanisms have been suggested to underlie virtual pain: (1) silencing of pyramidal neurons probably through activation of GABAergic interneurons (Haug et al. 1992), and (2) disruption of neural processing due to the addition of noise to the ongoing activity (Siebner et al. 2001; Di Lazzaro et al. 2004). The balance between these two mechanisms depends mainly on the stimulus intensity (Di Lazzaro et al., 2004) and on the intrinsic excitability of the neurons.

Among the excitatory amino acids released by the nociceptive afferents from the muscle in the subnucleus caudalis, glutamate plays a primary role. The release of glutamate leads the activation of caudalis nociceptive neurons by a process involving ionotropic receptors. The most important receptors are the NMDA and the alpha-amino-3-hydroxy-methyl-4-isoxazole-propionate (AMPA) receptors. These different types of glutamate receptor in the caudalis region have different physiologic characteristics and actions. Activation of the AMPA receptor is responsible for the transmission of mild nociceptive information and the activation is rapid and short lived. More intense and longer stimuli can cause the release of substance P by the central endings of primary afferents. Substance P acts on the neurokinin receptors and NMDA receptors are then available for glutamate. The result is prolonged, slow EPSPs that with temporal summation of nociceptive inputs

can maintain the second order neurons in a partly depolarized status so that they are more likely to fire action potentials (Murray and Peck 2010).

Once the nociceptive signal is generated, it propagates toward its first connection with second-order neurons in the subnucleus caudalis where another action potential is generated sending the nociceptive information to higher CNS centers. These second-order neurons are mainly wide dynamic range (WDR) neurons that respond to both noxious and non-noxious stimuli, and nociceptive specific (NS) neurons which respond only to noxious stimuli. Additionally, low threshold mechanoreceptor (LTM) neurons are present that respond to non-noxious stimuli. WDR neurons make up the majority of second-order neuron in the subnucleus caudalis and routinely receive nociceptive input from A-delta and C-fibers and non-noxious input from A-beta fibers. The name, wide dynamic range, originated from the fact that input from primary afferents in the skin, muscle, and visceral organs converge on these neurons that are able to respond to a wide range of stimulus intensities. When WDR neurons are activated by painful stimuli, they may become sensitized (central sensitization) leading to an expansion of receptive fields and radiation (spreading) of pain. Moreover, within the subnucleus caudalis there are interneurons that communicate with other interneurons to form a network. For example, projection interneurons are responsible for transmitting nociceptive information to higher centers in the brain from subnucleus caudalis. Interneurons also pass information to reflexmotoneurons resulting in a reflex response to nociception, such as the withdrawal of a hand from the heat of a flame. When pain perception occurs, the body responds by protecting itself from further tissue damage through various adaptive physiological responses. An increase in excitability of trigeminal second-order neurons results in enhanced sensory function to produce phenomena such as secondary hyperalgesia and allodynia. In addition, hyperalgesia and allodynia can also occur at the site of injury through sensitization of peripheral nociceptors; this is known as primary hyperalgesia and allodynia. These pain faciliatory responses make the individual more aware of either injury or potential injury, and encourage responses to guard and immobilize the injured part and protect it from additional injury. However, under certain circumstances the brain can go into survival mode completely suppressing pain transmission and perception through the activation of intrinsic pain inhibitory systems.

Masticatory Muscle Disorders

Masticatory muscle disorders are a group of musculoskeletal conditions that are the major cause of

nonodontogenic pain in the orofacial region. They include: masticatory muscle pain or myalgia, myositis, myospasm or trismus, myofibrotic contracture and neoplasia. Other conditions that can be classified as masticatory muscle disorders are muscle hypertrophy, muscle hyperplasia and movement disorders.

A meta-analysis involving 21 epidemiological studies and a total of 3,463 subjects with orofacial pain concluded that the overall prevalence for myofascial TMD pain (group I muscle disorder Research Diagnostic Criteria for Temporomandibular Disorders (*RDC/TMD*)) was 45.3%, whereas the prevalence of disc displacement (group II-RDC/TMD criteria) was 41.1% (Manfredini et al. 2011). Further, myofascial TMD is commonly comorbid with other conditions including headaches. In a recent study it has been reported that individuals with myofascial TMD were significantly more likely to suffer from chronic daily headaches (RR: 7.8; 3.1-19.6), migraine (RR: 4.4; 1.7-11.7), and tension-type headache (RR: 4.4; 1.5-12.6) in comparison to individuals without TMD pain (Slade et al. 2016). Table 1 summarizes the different conditions of the masticatory muscle disorders.

Muscle hypertrophy and hyperplasia

Hypertrophy refers to an enlargement caused by an increase in the size but not in the number of cells. Generalized masticatory muscle hypertrophy may affect the temporalis, masseter and medial pterygoid muscles in a variety of combinations. Masseter hypertrophy is commonly seen in late adolescence and early adulthood, and affects both males and females, but has slight male predominance (Sannomya, Goncalves and Cavalcanti 2006). Masseter muscle hypertrophy in itself has been postulated to be associated with awake and sleep bruxism as a possible result of prolonged tooth clenching (Manfredini et al 2013, Castroflorio et al 2015). Masseteric hypertrophy may present as either unilateral or bilateral painless swelling of unknown origin in the region of angle of mandible (Figure 2). This is in contrast to hyperplasia, which results in an increase in the number of fibers within a muscle. However masticatory muscle hyperplasia is very rare. Little on this condition has been reported in literature with the exception of the masticatory muscle tendon-aponeurosis hyperplasia (MMTAH) (Sato & Yoda 2016). MMTAH is a condition in which the tendon and aponeurosis of the bilateral masticatory muscles exhibit hyperplasia, thus restricting muscle extension. The main symptom of MMTAH is limited mouth opening. The etiology of MMTAH still remains unclear, although parafunctional habits are often associated with it. A hard

cord-like structure found along the anterior border of the masseter muscle on intraoral palpation can help in clinical diagnosis, although MRI can help visualize tendons and aponeuroses, the criteria for hyperplasia in these tissues have not yet been established. The definitive diagnosis between masticatory muscle hypertrophy and masticatory muscle hyperplasia can only be established by histology.

Myalgia

According to DC/TMD masticatory muscle pain or myalgia can be defined as a pain of muscle origin that is affected by jaw movement, function, or parafunction, and replication of this pain occurs with provocation testing of the masticatory muscles. Myalgia may be caused by: 1) direct muscular trauma or infection; or 2) muscular overuse as a result of parafunction or stress related primary myogenous pain. It can also be a secondary pain associated to temporomandibular joint diseases (Clark 2008).

Masticatory myalgia is further subdivided into three mutually exclusive subtypes: 1) local myalgia, defined as pain localized to the site of palpation; 2) myofascial pain, defined as pain spreading beyond the site of palpation but within the boundary of the muscle being palpated; and 3) myofascial pain with referral, defined as pain at a site beyond the boundary of the muscle being palpated. In order to establish a diagnosis of myalgia, the patient should report pain in the jaw, temple, in the ear, or in front of the ear, and aggravation of the pain with jaw movement, function or parafunction. In addition, the clinical evaluation should confirm pain localized to the temporalis or masseter muscles. Also, the fact that the pain induced by a specified provocation test replicates the pain and the patient has experienced pain over a period of time (typically the last 30 days) supports the diagnosis. Provocation tests include pain with opening jaw movements and palpation of the temporalis and masseter muscles. The palpation pressure to provoke this pain is 1 kg for 2 seconds. However, to differentiate the three subtypes of myalgia, the duration of the 1 kg of palpation pressure needs to be maintained for at least 5 seconds to elicit spreading or referred pain.

Myofascial pain is the most frequent diagnosis in patients with orofacial pain (42%), followed by disc displacement with reduction (32.1%) or arthralgia (30%) (Poveda-Roda et al. 2012). This disorder is clinically characterized by localized tender sites or TrPs in the muscle, tendon or fascia.

Myofascial TrPs, commonly known as TrPs, are described as hyperirritable spots in the fascia surrounding skeletal muscle. They are associated with palpable nodules in taut bands of muscle fibers (Travell et al. 1999). The TrP model states that unexplained pain frequently radiates from these points of local tenderness to broader areas, sometimes distant from the TrP itself. Compression of a TrP may elicit local tenderness, referred pain, or local twitch response. The local twitch response is not the same as a muscle spasm. This is because a muscle spasm refers to the entire muscle contracting whereas the local twitch response refers only involves a small microspasm, without contraction of the entire muscle. It is thought that TrP form as a local contraction in a small number of muscle fibers in a larger muscle or muscle bundle. These in turn can pull on tendons and ligaments associated with the muscle and result in pain deep within a joint(s). TrPs have an abnormal biochemical composition with elevated concentrations of acetylcholine, noradrenaline and serotonin and a lower pH (Shah and Gilliams 2008). Many TrPs have pain patterns that overlap, and some create reciprocal cyclic relationships that need to be treated extensively to remove them. Myofascial pain syndrome (MPS) is described as the sensory, motor, and autonomic symptoms caused by myofascial TrPs. The best available evidence supports that TrPs develop after muscle overuse. Several potential mechanisms may play a role, such as eccentric overload, submaximal sustained, and (sub)-maximal concentric contractions. A key factor is the local ischemia that leads to a lowered pH and a subsequent release of mediators in muscle tissue (Bron and Dommerholt 2012).

A recent review (Quintner et al, 2015) critically examines the evidence for the existence of myofascial TrPs stating that, to date, the theory of myofascial pain caused by TrPs remains a conjecture since it lacks external validity. This is not to deny the existence of the clinical phenomena themselves, for which logical and scientific explanations based on neurophysiological phenomena can be advanced. This review adds a few new hypotheses on the phenomena of myofascial pain caused by TrPs: the first one is that focal inflammation of peripheral nerves leads to ectopic axonal mechanical sensitivity and spontaneous discharge of some but not all the nociceptors within the inflamed nerve. These changes can be expected to lead to focal areas of neurogenic inflammation and possibly to sensitization in the muscle innervated. The second hypothesis is that nociception in deep tissues can induce the phenomena of remote localized pain and tenderness, relegating TrPs to being a site of secondary allodynia reflecting altered central nociceptive mechanisms. Due to this even the treatment of TrPs, in the authors' opinion, is questionable since

the vast majority of studies and meta-analyses do not support the prediction from myofascial pain theory that focal treatment of TrPs is effective.

The treatment of MPS focuses on analgesics and anti-inflammatory therapy, followed by physiotherapy, occlusal therapy, transcutaneous electric nerve stimulation (TENS), laser therapy, acupuncture and biofeedback (Paul et al. 2014). Physiotherapy should include deep stroking massage applied directly to the TrP that moves blood and lymph fluid with accumulated waste product from the painful areas and also brings relief by activating release of endorphins (Davies 2004). Psychological or psychiatric management should be incorporated to address the psychosocial factors that may be driving MPS (Lee et al. 2017).

Occlusal therapy involves the use of oral appliances (OAs). This approach has changed over the time. A recent review stated that OAs may be an effective treatment modality for some TMDs owing to their potential for acting as an elaborate placebo rather than any specific therapeutic mechanism.Evidence derived from clinical studies however suggests that OAs are more effective for treating myogenous TMD problems than they are for intracapsular conditions, but they can be helpful for both in properly selected patients. (Figure 3).

TENS therapy involves application of electrodes connected to a small battery-powered unit along the painful muscle and is a form of electroanalgesia. High frequency and high intensity TENS (100 hz, 250 ms stimulation followed by 100 hz, 50 ms) is effective in reducing myofascial pain without having any effect on local TrP sensitivity (Marchand et al. 1993) (Figure 4).

Low level laser therapy (LLLT) uses red and infrared light for the relief of pain, to accelerate healing and decrease inflammation. When the light source is placed against the skin, the photons penetrate several centimeters and get absorbed by the mitochondria, improving tissue repair and accelerating wound and tissue healing. Laser irradiation provides an analgesic effect by decreasing the spasm in muscle arterioles leading to increase in tissue oxygenation (Ozdemir et al. 2001). Effects on endorphin levels and the gate control of pain are two other mechanisms that may result in analgesia by laser radiation. Increase in oxygen supply to hypoxic cells in TrP areas by regulation of micro-circulation following LLLT has been reported to lead to functional recovery and decrease of spontaneous pain (Simunovic 1996) (Figure 5).

Acupuncture consists of two types of dry needling (DN): superficial DN, which penetrates only the skin and superficial muscle, and deep DN, which involves the insertion of a solid filiform needle directly into the TrP (Kalichman and Vulfsons 2010). Precise needling of the TrP provokes a local twitch response (LTR), a brief muscle contraction, which should be elicited for successful therapy (Hong 1994). DN and manual pressure technique on TrPs have shown no difference in the treatment of neck and shoulder myofascial pain (De Meulemeester et al. 2017).

Biofeedback therapy consists of behavior modification through cognitive behavioral therapy in order to make the patient self-conscious of muscular over-use (e.g. daily teeth clenching or incorrect body posture). Biofeedback supported by surface-EMG is a motor training resulting in performance improvements that are associated with cortical re-organization and adaptation of the behavior of motor-units (Iida et al. 2013). Training tasks and motor learning have been shown to influence the corticomotor projections in finger movements (Iida et al. 2013). In orofacial movements, some investigators have confirmed the plasticity of corticomotor pathways occurring 30 minutes post-training of repetitive tongue movements (Svensson et al. 2006). Another study (Bouderau et al. 2010) has demonstrated short term neuroplasticity of the corticomotor pathways related to the jaw muscles in relation to short term tooth clenching training. Therefore, visual biofeedback could be helpful in motor training of masticatory muscles improving muscle performance in terms of accuracy. No evidence supporting the use of visual biofeedback to induce muscle relaxation is available in existing literature.

As myofascial pain commonly results in clinical states such as increased muscle tension, muscle spasm, spasticity and TrP formation, the role of muscle relaxants in relieving pain is found to be beneficial. Tizanidine is a commonly used centrally acting muscle relaxant having alpha-2-adrenergic agonist properties, which decreases muscle spasm, and is thought to prevent release of excitatory amino acids by suppressing polysynaptic excitation of spinal cord interneurons. Tizanidine should be administered initially at bed time owing to its sedative effect with gradual dose increment from an initial dose of 2 to 4 mg at bedtime up to the maximum of 8 mg, 3 times/ day (Ketenci et al. 2009).

Other administered muscle relaxants are benzodiazepines. These drugs are centrally-acting

serotonin receptor antagonists that reduce muscle tone by inhibiting serotonergic descending systems in the spinal cord. Cyclobenzaprine is part of this family of drugs. At present, cyclobenzaprine is used in the clinical management of MPS in temporomandibular disorders to improve the quality of sleep and to reduce pain. A review of the literature suggests insufficient evidence to support the use of cyclobenzaprine in the treatment of MPS since the authors identified only two small studies in which a total of 35 participants were analyzed without any possible estimate of risks for benefit or harm.

Another class of drugs administrated in the treatment of MPS are antidepressant medications such as tricyclic antidepressants (TCAs). TCAs appear to be effective in the control of chronic orofacial pain of non-inflammatory origin, and include amitriptyline, doxepin, nortriptyline and desipramine. Common side effects include dry mouth, sedation, constipation and orthostasis (Pettengill and Reisner-Keller 1997). TCAs have a more predictably positive effect on sleep continuity and slow-wave sleep than the selective serotonin reuptake inhibitors (Sullivan and Robinson 2006).

A recent review on the use of drugs for chronic orofacial pain found that medications approved by the FDA for fibromyalgia (pregabalin, duloxetine, and milnacipran) are better than placebo but are not robust in their efficacy and are best judged as poor treatments. Fibromyalgia and widespread myofascial pain treatment will continue to involve combining medications with non-pharmacologic treatment methods, with the latter the preferred method of treatment. Lower-strength opioid therapy (eg, tramadol) is used with reasonable efficacy to help the most severely fibromyalgia syndrome–disabled patients. These medications may be considered for treatment of MPS refractory to other treatments.

i) Local Myalgia

Local myalgia is defined as pain of muscular origin that can be localized by palpation. Limitation of mandibular movements secondary to pain may be present (De Leeuw 2013). The diagnostic criteria to establish the diagnosis of local myalgia include a positive history for both: 1) pain in the jaw, temple, in the ear, or in front of the ear; and 2) pain modified with jaw movement, function or parafunction. In addition, examination of the temporalis or masseter muscle must confirm all of the following: 1) confirmation of pain location in the area of the temporalis or masseter muscle; 2) report of familiar pain during palpation of the temporalis or masseter muscle; and 3) report of pain

localized to the site of palpation.

Sometimes local myalgia will develop in response to a locally painful pathologic process, such as an acute joint inflammation or injury (protective muscle splinting / co-contraction), delayed post-exercise soreness, muscle fatigue, or pain from ischemia. Protective muscle splinting (protective co-contraction) is a normal physiological response of the musculoskeletal system. In the presence of an injury, the normal sequencing of muscular activation is altered in order to protect the vulnerable part from further injury. In the orofacial region, this response results in increased activity of the jaw opening muscles during closure, as well as an increase in closing muscles activity during opening. The etiology recognizes altered sensory or proprioceptive input, presence of constant deep pain input, and increased emotional stress. Pain can be evoked on palpation and function, and patients report a feeling of muscle weakness. In these cases, treatment should be directed toward the cause of the protective muscle splinting.

While protective muscle splinting represents a CNS-induced muscle response that can produce local myalgia when repeated over time, local myalgia also can result from alterations of the normal biochemical environment of muscular tissue. This is the initial response to overuse of the muscle or muscular fatigue and is thus termed local muscle soreness. The activity of groups III and IV afferents progressively increase during fatigue and protracted protective muscle splinting because of the release into muscles of metabolic products, such as bradykinin, substance P, prostaglandin, serotonin, and histamine (Castroflorio et al 2012). According to the pain adaptation model, the activity of thin nociceptive muscle afferents facilitates inhibitory pathways when the muscle acts as an agonist, and facilitates excitatory pathways during antagonist activity. Thus, smaller and slower movements are generated, which probably represents a functional adaptation to muscle pain. Local ischemia from muscular overuse, and subsequent fatigue, can result in the release of the aforementioned substances that cause allodynia.

The phenomena of a delay in the onset of muscle soreness after intense or unaccustomed use of a muscle is called delayed post-exercise muscle soreness (delayed onset muscle soreness: DOMS). The overuse results in interstitial inflammation and delayed pain in the muscles between 8-24 hours later and generally resolves within 3 to 7 days. Eccentric (lengthening) muscle contractions, observed for example in the right masseter muscle during forceful left lateral grinding movement,

can induce myalgia more easily than concentric contractions. Up to six hypothesized theories have been proposed for the mechanism of DOMS, namely: lactic acid, muscle spasm, connective tissue damage, muscle damage, inflammation and the enzyme efflux theories. However, an integration of two or more theories is likely to explain muscle soreness (Cheung et al 2003). Local myalgia develops, apart from locally painful pathologic process, even from muscle fatigue. Fatigue can be defined as a reduction of force-producing capacity of the neuromuscular system with prolonged activity (Asmussen 1979). Studies indicate that fatigue appears when depletion of energy stores occurs, accumulation of by-products or impairment of muscle contractile mechanism is attained in response to exercise, and recently its relation to an immunological and genetic response is suggested (Keyser 2010; Finsterer 2012). This fatigue and pain are short-lived once the contraction is stopped, as the jaw elevators have a high oxidative capacity (Svensson and Graven-Nielsen 2001). Ischemia as well as muscular fatigue produces little or no tissue damage, however nociceptive or physiologic pain can be expected. The acidic environment following muscular ischemia activates proton-sensitive channels like the acid-sensing ion channel (ASIC) and the transient receptor potential vanilloid 1 receptor (TRPV1).

Myositis

Myositis is a primary inflammation of muscle resulting from infection such as viruses, including the common cold, flu and human immunodeficiency virus (HIV) or trauma. It is characterized by constant acute pain and is usually accompanied by swelling, redness of the overlying skin and increased temperature over the affected muscle (Greene et al. 2013).

Myositis ossificans (MO) is the most common described myositis of the masticatory muscles. It is a rare disease involving heterotopic ossification in the muscle. The most accepted etiologic mechanism includes osteoblast stimulation as a consequence of bone or soft tissue damage causing formation of new bone, dystrophic calcification or calcified chondroid matrix. MO can be divided into two groups: 1) progressive MO and 2) traumatic MO.

Progressive myositis ossificans or Munchmeyer's disease (also called fibrositis ossificans progressiva or fibrodysplasia ossificans progressiva) is a hereditary form with autosomal dominant transmission (Figure 6). The genetic mutation affects a bone morphogenic protein receptor. Bone morphogenic proteins are regulatory proteins that play a critical role in embryology, bone formation

and fracture healing (Chen et al. 2004; Fiori et al. 2006;). This disease leads to the formation of a second (heterotopic) skeleton and it is the most catastrophic disorder of heterotopic ossification in humans (Sheth et al. 2014). It persists throughout childhood and early adult life and progressively immobilizes all the joints. There is no treatment for Munchmeyer's disease.

Myositis ossificans traumatica (MOT) is a more circumscribed form, which involves single muscles or muscle groups subjected to violent or repeated trauma (Spinzia et al. 2014) (Figure 7). It is frequently reported in the orthopedic literature, often involving the quadriceps femoris and brachialis anticus and seems to occur after significant blunt trauma, such as sport-related trauma or repeated minor injuries such in contact sports like soccer, or rugby and from falls. Masticatory muscles are seldom involved with less than 60 cases reported in the existing literature (Fitè-Trepat et al 2016). The longest series (42 cases) has shown a male predominance with a 2.5:1 ratio, and with an age range of onset between 38-48 years. The masseter muscle is the most affected, followed by medial and lateral pterygoid muscles, while the temporalis muscle is the least affected (Schiff and Meara 2013). A possible explanation for this incidence could be the surface location of the masseter and its exposure to possible direct trauma (Aoki et al. 2002). Despite trauma being the most likely etiology, the exact pathogenesis remains unclear. According to current data, a bone morphogenic protein signal from the point of injury induces mesenchymal cell differentiation into osteoblast or chondroblasts (Qian et al. 2015). As a result, pain and swelling, jaw dysfunction, particularly limited range of motion and pain on movement, are characteristic features of MOT.

Diagnosis is made by clinical, radiological and histological study. Myositis can be differentiated from other forms of myalgia by its acute presentation and constant nature of the reported pain, its associated sequela such as, the patient's acute and unambiguous responses to muscle palpation, and a history of recent trauma or infection (Lundberg and Vencovsky 2017). CT scan is the most useful imaging modality as it shows a well circumscribed lesion with high-attenuating periphery and a low-attenuating central portion within muscle or soft tissues (Figures 6 and 7). Histological examination highlights an inner zone of proliferating fibroblasts and mitotic activity, an intermediate zone of developing osteoid cells and collagen trabeculae, and an outer zone of mature bone separated from the surrounding muscle by connective tissue without inflammatory infiltrate (Fitè-Trepat et al 2016) (Figure 8). Surgical excision of the entire lesion is a reasonable treatment option. Spontaneous resolution has been reported in about one third of cases (Schiff and Meara

2013).

Myospasm

Myospasm, often referred to as a muscle cramp, is an acute but rare condition resulting from a sudden, involuntary, and continuous tonic contraction of a muscle or muscles. It is characterized by localized acute pain and severely limited range of motion of the mandible (Gonzales and Mohl 2006). Acute malocclusion is common in these patients and it results from a sudden change in the resting length of a muscle that controls jaw position (Okeson 2012). Treatment should be directed toward the elimination of the disorder rather than directed toward correcting the malocclusion.

The etiology appears to be related to continued deep pain input, local metabolic factors within the muscle tissue associated with fatigue or overuse (e.g. awake and sleep bruxism) (Castroflorio et al 2012b, 2012c) and idiopathic myospasm mechanisms (Okeson 2015).

Masticatory myospasm can be classified into jaw closing and jaw opening types. Jaw closing type involves masseter and temporalis muscles, while jaw opening type involves the inferior lateral pterygoid muscles (Fu et al. 2012). Masseter and/or temporalis myospasm is characterized by 1) limited mouth opening and 2) acute pain. On the contrary, inferior lateral pterygoid myospasm is characterized by 1) difficulty in jaw closing after wide opening and 2) involuntary jaw movements (Cao et al. 2012). However, a definite diagnosis could be obtained only with needle electromyography into the affected muscles.

Treatment of myospasms includes pain reduction by ice (vapocoolant spray) or injection of local anesthetic (2% lidocaine without vasoconstrictors) into the muscle in spasm (Figure 9). Once the pain is reduced, the affected muscle may be stretched to full length. When clear etiologic factors have been identified, attempts to eliminate these factors should be made. If myospasms are secondary to fatigue and overuse, the patient is advised to rest their jaw. If myospasms are chronic or recurrent without identifiable etiologic factors, the condition may represent an oromandibular dystonia and further investigation is necessary.

Myofibrotic contracture

This condition often occurs as a consequence of an inflammatory process leading to fibrous changes

in the muscle or its sheath. The disorder follows an infectious process or traumatic myositis, particularly if the patient has experienced a long period of limited range of movement or masticatory dysfunction. Radiation therapy, incision through a muscle with fibrotic healing and disuse for long period (>6 weeks) can result in myofibrotic contracture (Figure 10). This condition, although not painful, can result in a limited jaw opening with resistance to passive stretching. Myofibrotic contracture is irreversible and requires surgical detachment for a patient whose function is severely impaired (Benzon and Raj 2008).

Movement disorders

Movement disorders are defined by clinical sign and symptom patterns (syndromes) in which normal functional movements are altered. Involuntary movement disorders (dyskinesias) can be classified as hypokinesias or hyperkinesias.

Hypokinesias

Hypokinesia refers to decreased bodily movement, characterized by a partial or complete loss of muscle movement due to a disruption in the basal ganglia (Van Hilten et al. 1994).

Parkinson disease and parkinsonian syndromes

Parkinson disease is recognized as one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years. The disease is the prototypical bradykinesia syndrome producing a progressive movement disorder. Parkinson disease is predominantly a disorder of the basal ganglia. The basal ganglia motor circuit modulates the cortical output necessary for normal movement. Parkinson disease and other syndromes producing parkinsonism may be initially indistinguishable. Possible causes of parkinsonism include multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration. The combination of patient history, clinical examination, computerized tomography and/or magnetic resonance imaging evaluations and laboratory assessment, can help to distinguish among Parkinson disease and parkinsonism. Most substantially, a strong clinical response to levodopa in patients for whom other causes have been eliminated is a good indicator of Parkinson disease. No specific, standard criteria exist for the neuropathologic diagnosis of Parkinson disease, as the specificity and sensitivity of its characteristic findings have not been clearly established. However, the two major neuropathologic findings in

Parkinson disease include 1) loss of pigmented dopaminergic neurons of the substantia nigra pars compacta, and 2) the presence of Lewy bodies and Lewy neurites. Lewy bodies are abnormal aggregates of protein that develop inside nerve cells. The loss of dopamine neurons occurs most prominently in the ventral lateral substantia nigra. Approximately 60-80% of dopaminergic neurons are lost before the motor signs of Parkinson disease emerge.

The etiology of Parkinson disease is still unclear; however, the accepted hypothesis is that a combination of genetic and environmental factors are involved. Environmental risk factors include use of pesticides, living in a rural environment, exposure to herbicides, and proximity to industrial plants. Risk seems to increase with length of exposure (Anderson 2013; Pezzoli and Cereda 2013).

The clinical signs of interest in the jaw muscles are represented by:

1) resting tremor of the head, lips and facial muscles;
2) bradykinesia resulting in slow mastication and slow movements of the head on request;
3) rigidity may restrict jaw and head movements;
4) forwarded head posture;
5) excessive saliva production;
6) in more severe cases the patient's face becomes mask-like.

Before the introduction of levodopa, Parkinson disease caused severe disability, or death in 65% of patients within 10 years. The mortality rate from Parkinson disease was 3 times that of the general population matched for age, sex, and racial origin. With the introduction of levodopa, the mortality rate dropped approximately 50%. This is thought to be due to the symptomatic relieve provided by levodopa, as no clear evidence suggests that levodopa stems the progressive nature of the disease (Grimes et al 1999; Thobois et al. 2005).

Hyperkinesias

Hyperkinesia refers to an increase in muscular activity that can result in excessive abnormal movements, excessive normal movements, or a combination of both (Anthoney 1994).

Dystonia

Dystonia is characterized by involuntary sustained muscle contractions affecting one or more sites of the body, frequently causing twisting and repetitive movements or abnormal postures (Fahn et al. 1998). Dystonic muscle contractions are sustained, unidirectional and formed in a clear pattern. Dystonias are centrally mediated and differ from common muscular spasms and cramps induced by overwork and hypoxia. Specific information on the prevalence of dystonia is lacking as the existing epidemiological studies of the condition have adopted different methodologies for case ascertainment, resulting in widely differing reported prevalence. The prevalence estimates for primary dystonia range from two to 50 cases per million for early-onset dystonia and from 30 to 7320 cases per million for late-onset dystonia (Defazio et al. 2004).

Dystonias may have an onset at any time during life and many of them present with a genetic origin: they are most frequently seen in individuals of Eastern European Jewish origin and in Mennonites. Although young individuals generally have symptoms in the extremities, adult-onset dystonia more often affects the head and neck.

Oromandibular dystonia

This disorder produces involuntary contractions of masticatory muscles, the suprahyoid muscles and/or the intrinsic tongue muscles. The patient exhibits ocular blinking, tooth grinding and grimacing. Such involuntary contractions can be rigid and painful. Oromandibular dystonia has been associated with impaired movement-related cortical potentials, indicating a cerebral cortex component of the disease (Yoshida et al. 2003) (Figure 11).

Assessment of dystonia is not straightforward (Del Sorbo et al. 2015). Rating scales developed for different focal forms show remarkable differences. Recommended scales are available for cervical dystonia, blepharospams and laryngeal dystonia. By contrast, anecdotal (not fully clinimetrically validated) scales are available for oromandibular and arm dystonia (Albanese et al., 2013).

Treatment of dystonia includes medication with motor-suppressive medications (e.g. cholinergic receptor antagonists or blockers, and GABA-ergic including benzodiazepines), botulinum toxin (BoNT) injection, intrathecal baclofen, surgical interventions such as the globus pallidus internus deep brain stimulation, acupuncture, rehabilitation, and psychotherapy. Oral medication is usually an adjunct to more potent therapeutic options except for some specific indications like dopa-

responsive dystonia. Botulinum toxin is usually the treatment of choice for focal dystonia. Deep brain stimulation can be considered for both focal and non-focal phenotypes of dystonia (Mezaki 2011).

Hemifacial spasm (HFS)

Hemifacial spasm represents a segmental myoclonus of muscles innervated by the facial nerve. The disorder presents in the fifth or sixth decade of life, almost always unilaterally, although bilateral involvement may occur rarely in severe cases. Hemifacial spasm generally begins with brief clonic movements of the orbicularis oculi and spreads over years to other facial muscles (corrugator, frontalis, orbicularis oris, platysma, zygomaticus) (Abruzzese et al. 2011). Symptoms of hemifacial spasm are similar to facial dystonia but the spasms are usually less variable than many focal dystonias, although some of those affected do find that their condition worsens under stress and improves when lying down.

Studies have shown that the most effective method of hemifacial spasm screening is with MRI (Figure 12). In one study, only 25% of the CT scans showed the vascular abnormality in the CNS (e.g. angioma, vertebrobasilar abnomalitieses, and vascular compressions of facial nerve) in hemifacial spasm patients, whilst more than half of the MRI imaging demonstrated a vascular anomaly (Arita et al. 2012, Park et al. 2015, Tan et al. 1999). MRI imaging should be the initial screening procedure in the assessment of patients with hemifacial spasm (Yaltho and Jankovic 2011). Microvascular decompression (MVD) is the most effective treatment for hemifacial spasm (Zhang et al. 2017, Zhi et al. 2017), together with BoNTs (Prutthipongsit and Aui-aree 2015; Sorgun et al. 2015).

Choreas

Chorea is an abnormal involuntary movement characterized by brief, abrupt, irregular, unpredictable, non-stereotyped movements (Hao et al. 2015). They can affect various body parts, and interfere with speech, swallowing, posture, and gait. Chorea may worsen with anxiety and voluntary movements, and subsides during sleep. When it occurs with athetosis (a more distal, slower, writhing, abnormal movement), it is known as choreoathetosis. In more severe choreiform movements, these appear wild, violent, and may involve flinging of a body part and induce injuries, and is known as ballism. Chorea may also occur with other abnormal movements such as dystonia.

There is a wide range of seemingly unrelated causes, from pregnancy (chorea gravidarum) to inherited forms such as Huntington's disease and benign hereditary chorea, infection/immune-related such as Sydenham's chorea, and systemic lupus erythematosus, focal vascular lesions in the basal ganglia, drugs such as levodopa, neuroleptics and oral contraception, various metabolic and endocrinological disorders such as hyperthyroidism, hypo/hyperparathyroidism and hypo/hyperglycemia (Kavtaradze and Mosidze 2007). Its pathophysiology involves a functional dysregulation of the basal ganglia motor circuit, where the final thalamo-cortical output is increased, resulting in increased movement and chorea. Treatment of chorea usually entails addressing its etiology. The most common symptomatic treatment of chorea includes the use of neuroleptic agents, other dopamine depleters, such as tetrabenazine, and sometimes benzodiazepines (Burgunder and Guttman 2011, Reilmann 2013).

Tics

A tic is a non-voluntary body movement or vocal sound that is made repeatedly, rapidly, and suddenly. It has a stereotyped but non-rhythmic character. Tics are categorized as motor or vocal, and as simple or complex. The American Psychiatric Association (APA) defines four tic disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association 2013). Disorders are distinguished from one another according to three criteria: the age at onset; the duration of the disorder; and the number and variety of tics, and includes transient tic disorder, chronic motor or vocal tic disorder, Tourette disorder (aka Tourette syndrome), and tic disorders not otherwise specified.

Tic disorders have a high rate of comorbidity with other childhood disorders. The frequencies of the most common disorders that may be comorbid with tic disorders and Tourette syndrome (TS) include (Bitsko et al. 2014):

- attention-deficit/hyperactivity disorder (ADHD): 50% comorbidity with tic disorders, 90% comorbidity with TS
- obsessive-compulsive disorder (OCD): 11% and 80% respectively
- major depression: 40% and 44 % respectively.

Other psychiatric problems that often coexist with tics and tic disorders include learning disorders, impulse control disorders, school phobia, sensory hypersensitivity, and rage attacks (Gadow et al. 2002). Neuroimaging studies have shown that tic disorders are related to abnormal levels of dopamine, serotonin, and cyclic AMP in certain parts of the brain (Malisza et al. 2011). No

medications are currently available to cure a tic disorder. Psychotherapy for tics and tic disorders typically involves education about tic disorders and therapy for the family as well as individual treatment for the child. Cognitive-behavioral approaches are the most common type of individual psychotherapy used to treat tics and tic disorders.

Bruxism

Bruxism is a repetitive jaw-muscle activity characterized by teeth clenching or grinding and/or mandible bracing or thrusting presenting two distinct circadian manifestations: sleep bruxism (SB), or awake bruxism (AB) (Lobbezoo et al. 2013). While AB is a semi-voluntary "clenching" activity influenced by stress and anxiety, SB is a stereotyped movement disorder occurring during sleep.

Bruxism can result in detrimental effects on the stomatognathic system namely teeth and resoration chipping and fractures. These are common and costly occurrences that happen all too often due to both AB and SB (Glaros et al. 2015). Bruxism is a common phenomenon in children, particularly as deciduous and secondary dentition erupt. It seems that most self-identified adult bruxers, were also bruxers as children (Carlsson et al. 2003). The activity of bruxism results in muscle hyperactivity, particularly in the masseteric sling muscles (masseter and medial pterygoid) and the lateral pterygoids. Therefore, myalgia can be the result of this activity (Glaros et al. 2015).

AB is linked to emotional and psychological stress (Okeson 1998, Shetty et al. 2010, Thompson et al. 1994). AB can exacerbate TMD symptoms such as headaches, muscle and joint pain and jaw locking (Glaros and Williams 2012, Goldstein and Clark 2017, Kalaykoya et al. 2011). AB is occasionally reported in Huntington's disease, primary dystonia, and secondary dystonia; however, its highest incidence and severity is reported in syndromes combining stereotypies and cognitive impairment, such as Rett's syndrome (97%), Down syndrome (42%), and autistic spectrum disorders (32%).

Treatment of AB is aimed at minimizing damage to teeth and restorations. Patient education is prudent (Goldstein and Clark 2017). Once aware of AB, the patient can commence habit awareness and modification strategies to address the AB. These may include reminder stickers focusing the patients' attention on occlusion, relaxing the mandible and avoiding teeth contact. If these changes are not successful, the use of a daytime OA may be recommended to prevent damage and promote

awareness of AB. Compliance with the use on an oral appliance during the day can be an issue (Glaros 2008).

SB is related to sleep arousals and has a combination of different motor activities including tooth grinding. It is classified as a centrally mediated movement disorder related to sleep characterized by involuntary phasic (rhythmic) or tonic (sustained) motor activity in the masticatory muscles (e.g. masseter, temporalis) during sleep. The prevalence of SB is the highest in childhood at approximately 14% to 20%. It stabilizes at around 8% to 12% in teenagers and adults, and decreases to 3% with aging (Castroflorio et al. 2015; Machado et al. 2014).

The pathophysiology of SB is unknown. It is considered multifactorial with potential influences of the central nervous system (CNS) (Manfredini and Lobbezoo 2009). Multiple risk factors have been associated with SB (Feu et al. 2013). In children, the most relevant risk factor associated to SB is the presence of sleep disturbances, such as sleeping for less than 8 hours a night, light and noise in the room (Castroflorio et al. 2015a).

In adolescents, a higher percentage of SB has been found in male adolescents with crowding (38%) (Katoka et al. 2015). The relationship between SB and malocclusion has been investigated over many years. Although some dentists suggest that malocclusion may cause SB, a recent review concluded that there is no evidence for a causal relationship between SB and occlusion (Lobbezoo et al. 2012).

Painful temporomandibular disorders (TMD) have a prevalence of 25.5% in a sample of European adolescents, and TMD pain was associated with sleep bruxism (O.R. 1.8) (Fernandes et al. 2015). Similar prevalence was reported for a sample of Brazilian adolescents with a significant association between sleep bruxism and TMD pain (OR. 2.02) (Rossetti et al. 2008). In adolescents, sleep disturbances such as snoring, nocturnal awakenings, obstructive sleep apnea (OSA) presented the strongest association with SB, while very few occlusal features had a moderate association. From a clinical point of view, investigation of sleep disorders such as snoring and OSA may provide insight into SB among adolescents (Castroflorio et al. 2016).

Polysomnographic (PSG) studies have demonstrated that SB is part of autonomic nervous system arousals occurring during sleep (Lavigne et al. 1996, 2008). Surface electromyographic (sEMG) recordings of the masseter and/or of the temporalis muscles show that SB features a typical muscular activation pattern, called rhythmic masticatory muscle activation (RMMA) which are usually associated with sleep arousal, occurring in a sleep period characterized by a dominance of autonomic sympathetic cardiac activity (Lavigne et al. 2011, Mayer et al. 2016).

Although many strategies have been proposed over the years to diagnose bruxism, the greater majority of data comes from studies adopting self-reported bruxism, which is only suitable to indicate "possible" bruxism at best. Such an approach is in contrast with the proposed standards of reference for bruxism diagnosis, which require definite measurements. Although PSG remains the current standard of reference for diagnosing SB, it has some disadvantages such as high cost, the amount of time needed for manual/visual scoring, the laboratory setting, not providing information of oral behaviors occurring in the home environment, and the potential for bias due to the examiner's skill. As a consequence, PSG is mainly used for research purposes. Thus, SB diagnosis in the clinical setting is mainly a clinical diagnosis based on the international diagnostic criteria proposed by the American Academy of Sleep Medicine (AASM) (American Academy of Sleep Medicine 2014) (Table 2). In the last few years some interesting portable devices have been introduced in order to ease data gathering. Portable devices adopting a combined electromyography (EMG) and electrocardiographic (ECG) recordings show an increased accuracy with respect to the EMG-based devices and may represent a promising, simple tool for the diagnosis of SB (Castroflorio et al. 2014, 2015b; Deregibus et al. 2014; Manfredini et al. 2013b) (Figure 13).

Treatment of SB is still lacking and there is inadequate evidence to define a standard of reference approach for the treatment of SB, with exception of the use of oral appliances (OAs) (Manfredini et al. 2015). It appears that most OAs are somehow effective in reducing SB activity at least in the short-term. This may suggest the existence of a potential 'novelty-effect' associated with the use of an OA, which leads to a reduction in sleep-time masticatory muscle activity, possibly due to transient reorganization motor unit recruitment.

Neoplasms

The masticatory muscles can be sites of benign (eg, rhabdomyoma) or malignant (eg,

rhabdomyosarcoma) or metastatic neoplasms. Some of them can be painful and depending on the location, they can produce spasm, limited mouth opening, and/or sensorimotor changes (eg, paresthesias) (De Leeuw 2013). Muscle neoplasms can lead to deviation of the mandible and acute malocclusions. Tumors of the masticatory muscles often result in swelling and thus they must be differentiated from adaptive muscle hypertrophy, parotid gland swellings, enlarged lymph nodes or any other regional swelling. Diagnostic imaging and biopsy are essential when a neoplasm is suspected.

Rhabdomyoma

Rhabdomyomas are particularly rare benign tumors of soft tissue, originating from skeletal muscle cells and accounting for only 2% of skeletal muscle tumors (Agamanolis et al. 1986) (Figure 14). They are mesenchymal tumors composed of striated muscle cells and topographically differentiated into cardiac and extracardiac types (Weiss and Goldbl 2001). The more common cardiac rhabdomyomas are often multiple and are most often encountered in children. They are usually associated with congenital abnormalities like tuberous sclerosis (50% of cases), phacomatosis or disorders of glycogen metabolism. Extracardiac rhabdomyomas are further classified into fetal, juvenile, and adult types (Fanburg-Smith et al. 2009). The separation of these different types of rhabdomyomas is based on their histologic appearance rather than the age of the patient. With respect to fetal rhabdomyomas which are generally solitary lesions, adult rhabdomyomas are multifocal in a percentage ranging between 3% and 10%. Furthermore, they occur almost exclusively in the head and neck region (93% of all cases), particularly in the larynx and pharynx of adult men (male-female ratio 3:1). Rhabdomyomas usually present as a slow-growing and painless cervical mass. Some of the associated symptoms reported in the literature are airway obstruction, hearing loss, dysphagia, hoarseness, and odynophagia. Pathogenetically, rhabdomyomas of the head and neck region are believed to originate from skeletal muscles of the third and fourth branchial arches (Weiss and Goldbl 2001). Due to the low occurrence of extracardiac rhabdomyomas their radiological appearance has not been well described. Computed tomographic scans and or magnetic resonance images may be both used to determine characteristics, extent of local involvement and possibility of multifocality. On T1- and T2- weighted MRI rhabdomyoma is isointense or slightly hyperintense to muscle. Their submucosal location and the absence of invasion into surrounding tissue may help to distinguish this kind of neoplasm from malignant ones. Nevertheless, imaging alone is not sufficient for a diagnosis (Koutsimpela et al. 2008). Adult rhabdomyomas are not

known to regress spontaneously or to have an association with tuberous sclerosis.

Treatment consists of conservative surgical excision. Macroscopically the neoplasm is well circumscribed or encapsulated. The consistency is soft, the color tan to grey and the cut surface is coarsely lobulated. The light microscopic appearance of adult rhabdomyomas are relatively reproducible, with polygonal close-packed cells with central or peripheral prominent and plentiful nuclei; pronounced eosinophilic, granular, glycogen rich cytoplasm and extensive vacuolization in some cells. Mitoses and necrosis are absent (Koutsimpela et al. 2008). The immunohistochemical features include cytoplasmic positivity for muscle-specific actin, desmin and myoglobin (Wenig 2008). Rhabdomyomas are mainly differentiated from granular cell tumors and recurrences have been described. Malignant transformation of these tumors has not been reported (Figure 15).

Rhabdomyosarcoma

Rhabdomyosarcomas (RMS) are a group of soft-tissue malignant tumors with a mesenchymal origin, which arise from cells committed to a skeletal muscle lineage that initiate myogenic differentiation but fail to disconnect from their proliferative cycle. These tumors affect children and adolescents (Franco et al. 2013) (Figure 16). RMS account for approximately 60% of sarcomas in children under 15 years of age (Dagher and Helman 1999). The reason is probably represented by the fact that these neoplasms are related to somatic development alterations. The head localization is the most frequent (35% of all cases).

The International Classification divides RMS into three histological subgroups with different prognoses: the embryonal subtype with two variants, i.e. spindle cell and botryoid, with a better prognosis; the alveolar subtype; and unspecified RMS with a poor prognosis (Newton et al. 1995). The 2013 World Health Organization (WHO) classification of skeletal muscle tumors modified the histologic classification of RMS to include sclerosing RMS as a type of spindle cell RMS separate from embryonal RMS (Fletcher et al. 2013). Most RMS are sporadic, and there is no evidence of risk factors, although a small subgroup is linked with familiar syndromes such as neurofibromatosis and Li-Fraumeni syndrome (Dantonello et al. 2008). The Surveillance Epidemiology and End Result (SEER) registry reports that one third of head and neck RMS affect adults (20–55 years, 23.1%; >55 years, 8.1%) with no gender bias, where the main localization was a parameningeal site with the embryonal histological subtype (Franco et al. 2013).

Clinical signs are variable and insidious. Most frequently the neoplasm appears as a painless mass. Differential diagnosis should always be performed when observing unilateral enlargement of masseter muscle. A masseter mass associated with ipsilateral lymphadenopathy is typically consistent with an underlying infectious disease (eg epidemic parotitis) or a malignant neoplasm like non-Hodgkin's Lymphoma. Imaging is not specific; whereby on CT scans these tumors appear as homogeneous, well-circumscribed, round to ovoid masses which are isodense to muscle (Figure 16). Biopsy is thus necessary to establish the diagnosis. Fine needle aspiration biopsy does not provide sufficient tissue. Excisional biopsy is appropriate if surgical removal can be achieved without significant damage to vital structures. Central to the diagnosis is the demonstration of rhabdomyoblasts via light microscopy, immunohistochemistry and/or electron microscopy. By light microscopy, the embryonal subtype is characterized by spindle-shaped cells in various stages of differentiation with highly eosinophilic cytoplasm (Figure 17). The alveolar subtype exhibits small, round, densely appearing cells that are loosely arranged, with septae that are similar to the alveoli of the lung. The botryoid variant is defined by the presence of subepithelial aggregates of tumor cells and is named due to the common "grape-like" appearance of these cells. Immunohistochemistry helps to identify skeletal muscle proteins, such as alpha-actin, myosin, desmin and myoglobin (Ben Slama et al 2009). Protocols used include surgical excision, radiotherapy and chemotherapy providing a 5-year survival rate greater than 80%.

Rare infections related to muscular orofacial pain

Cysticercosis

Cysticercosis represents infestation caused by the larval stage of the tapeworm, *Taenia solium* (Kumar et al. 2004). In the life cycle of the cestode, humans serve as either a definitive or an intermediate host. The life cycle of *T. solium* is complex requiring two mammalian hosts: a definitive host, in which the worm reaches sexual maturity, and an intermediate host, through which it propagates further. Humans are the only definitive hosts for adult *T. solium*. Disease is acquired by consumption of inadequately cooked pork. Pigs serve as natural intermediate hosts. Cysticercosis is an endemic disease in developing countries seen extensively in India, Indonesia, China, Africa, Peru and Mexico (Berkow 1992). Cases occur occasionally in non-endemic areas. Oral cysticercosis is very rare and may remain clinically asymptomatic. Reported prevalence of oral cysticercosis is 4.1% (Nigam et al. 2001). Cysticercosis can affect any part of the body, but most

commonly the central nervous system which has the most serious outcome. The most frequent sites of cysticercosis are subcutaneous tissue, brain, muscles, heart, liver, lungs and peritoneum. Common sites of involvement in the oral region are tongue (42.15%), buccal mucosa (18.9%), lips (26.15%) and masseter and temporalis muscles (Rastogi et al. 2013). Although pain is not a frequent feature, it has been reported in secondarily infected cases (Myshra et al. 1988). Differential diagnosis of a solitary lesion in the masseter muscle includes inflammatory lesions of the parotid gland, neoplasms of accessory parotid gland, parotid gland obstruction, preauricular lymphadenopathy, primary and metastatic tumors of masseter muscle, sarcoidosis, intramuscular lipomas and solitary neurogenic tumors such as neurilemmoma, neurofibroma and vascular lesions such as hemangioma or lymphangioma (Figure 18). Results of laboratory, serological and imaging studies narrow the differential diagnosis, however specific serological tests are not universally available. Cysticercal larvae often gradually reduce in size with capsular thickening and end-stage calcification. Imaging plays a critical role in diagnosing cysticercal involvement in the muscles. In a clinically symptomatic patient presenting with swelling in the oral and maxillofacial region, sonography provides a valuable clue to the likely nature of disease, pointing to cysticercal involvement. High-resolution sonography may prove to be a one-stop solution providing all necessary details in one examination, if a classical appearance is demonstrated. On sonographic examination, cysticercosis is described to have four patterns (Mittal et al. 2008). Lesions are generally non-vascular on Doppler examination.

Occasionally, further imaging by MRI may be needed when sonographic observations are non-specific. MRI appearances are not extensively reported in masseteric cysticercosis (Kumar et al. 2011). However, MRI examination is certainly a high-value examination in the evaluation of intracranial involvement, which is a relatively common site of involvement in cysticercosis (Santos et al. 2013). The cystic component of a larva is often demonstrated, in T2 weighted sequences, short tau inversion recovery (STIR) and diffusion-weighted imaging (DWI). The outline can be distorted owing to larval death. Cysticercal larvae are generally oriented along the long axis of the muscle, along masseteric fibres. Contrast enhancement extends beyond the lesion to the adjacent muscle fibres and also to regional lymph nodes. Laboratory evaluation by serology and the larval antigen, if available, may be confirmatory for diagnosis. The management of cysticercosis is conservative with chemotherapeutic agents: praziquantel and albendazole are the two cestocide drugs currently used for treatment.

Tuberculous Pyomyositis

Tuberculous pyomyositis should be considered in the differential diagnosis of immunosuppressed patients with fevers and myalgias (Stevens et al. 2005). Pyomyositis is a purulent infection of muscle that is generally the result of hematogenous spread. Typically, the infection is known to occur in the tropics in otherwise healthy individuals with no comorbidities. The most common organisms implicated in pyomyositis include *Staphylococcus aureus* as well as, increasingly, methicillin-resistant staphylococcus aureus (MRSA). Group A streptococci are also common with gram-negative bacilli and pneumococci, with non-group A streptococci occurring less often. There have also been instances of mycobacterial-induced pyomyositis (Wang et al. 2003). Typical presentations of pyomyositis involve fever and pain localized to a muscle group, generally the lower extremities. Orofacial manifestation are rare and related to extrapulmonary tuberculosis (TB), occurring in approximately 0.1–5% of all TB infections (Jain and Jain 2014). Orofacial TB can involve any site of the oral cavity and associated structures such as tongue, palate, lips, oral mucosa, jaw bones, sinuses, and temporomandibular joint.

The infection usually progresses in three stages. Stage one tends to be characterized by fever, muscle pain, and swelling. Stage two is where most patients present and occurs 10–21 days after initial symptoms begin. It is characterized by fever, muscle tenderness, and leukocytosis. Aspiration of the area will yield purulent material. Finally, stage three is the most severe and is accompanied by systemic toxicity. As a result, patients can develop complications of bacteremia. Diagnosis is typically made by radiography, predominantly by CT, and culture (Struk et al. 2001). MRI may also be helpful, especially in tuberculous pyomyositis (Soler et al. 2001). Because pyomyositis arises from hematologic spread, cultures, both from blood and drainage specimens, are extremely useful for determining appropriate antibiotic use. Treatment is dependent on the stage of the disease with stage 1 being treated with antibiotics. Stages 2 and 3 require both drainage as well as antibiotic treatment. Drainage is typically CT guided, but in the face of extensive disease, surgical intervention may be necessary.

Chronic pain in masticatory muscles

Chronic pain is now defined arbitrarily as pain lasting longer than 3 months (Treede et al. 2015). The new proposed classification of chronic pain by the International Association for the Study of

Pain (IASP) and International Classification of Diseases (ICD) lists myalgia and myofascial TMD pain with referral as examples of chronic pain in the orofacial region. Furthermore, there should be at least 50% of the days in a month with pain. Besides these criteria for duration and frequency, the clinical characteristics are similar to the DC/TMD criteria, such that patient-based reports of pain on jaw movements and pain in areas confirmed to originate from the jaw muscles, in addition to the important feature of jaw movements or palpation leading to a familiar pain sensation.

Although the DC/TMD distinguishes between myalgia and myofascial pain with spreading and with referral, the underlying differences in terms of mechanisms are not well-understood. Importantly, there seems so far to be no therapeutic consequence of a differentiation between myalgia and myofascial pain with referral. Interestingly, recent studies and experimental observations indicate that referred pain and sensations can be triggered with acute, intense painful stimuli (e.g. injections of hypertonic saline or strong mechanical stimuli) questioning if referred pain is a unique feature related to central sensitization in chronic muscle pain conditions. Rather, referred pain could represent an epiphenomenon of deep musculoskeletal pain. Nevertheless, chronic TMD muscle pain may be the consequence of both peripheral sensitization, central sensitization and the balance between endogenous inhibitory and faciliatory pathways (Kindler et al. 2011). Descending modulation has been speculated to contribute significantly to the chronification of pain because some studies in chronic TMD pain have indicated less efficient conditioned pain modulation although not all studies support this finding (Oono et al. 2014; Kothari et al. 2015). Further studies are needed to address the important question if impaired endogenous pain modulation is a risk factor for development of chronic TMD muscle pain or if TMD muscle pain, as it becomes chronic, causes a decrease in the endogenous pain modulatory systems.

Basic research efforts have emphasized the significance of protons for the transition of acute to chronic muscle pain (Sun and Chen 2016). This is based on nociceptor priming leading to dramatic intracellular changes with shifts from Protein Kinase A (PKA) to Protein Kinase C (PKC) systems and involving ASIC channels and TRPV1 receptors. Elegant studies have demonstrated that following a first exposure to protons (i.e. tissue acidosis), the nociceptor becomes primed for an extended period of time and if a second noxious event occurs, the intracellular changes lead to an exaggerated and prolonged response in terms of hyperalgesia. This is an attractive model to explain the transition from acute to persistent pain states and clearly together with peripheral and central

sensitization could play a significant role in the chronification of TMD muscle pain. Notwithstanding the significance of such basic research findings, the clinical challenge is the difficulty to translate such findings to humans. For example, experimental human pain studies with injections of low pH solutions repeated 3 days apart do not demonstrate any long-lasting excitation or sensitization of jaw muscles (Castrillon et al. 2013). Given there are multiple receptors and ion channels on muscle nociceptors, perhaps it is the combinations and interactions between these receptors that will be important for the chronification of muscle pain. Some studies have indeed indicated significant interactions between peripheral glutamate-sensitive receptors, low pH and temperature (Sato et al 2015, 2016). Furthermore, the serotonergic system is clearly involved in chronic TMD muscle pain in addition to dopamine (Dawson et al. 2016), interleukins 1-beta, 6, 10 and TNF-alpha (Park and Chung 2016) and omentin-1 (Harmon et al, 2016). It may be difficult to pin-point only one receptor system or pathway as the main one responsible for chronic TMD muscle pain.

Furthermore, the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) studies and other cross-sectional studies have clearly identified multiple risk factors associated with TMD pain (Slade et al. 2016). Not surprisingly these factors include numerous psychosocial factors (depression, anxiety etc), somatosensory factors, autonomic factors, clinical factors and genetic factors (Svensson and Kumar 2016). The OPPERA studies have also attempted to rank individual risk factors for first onset TMD pain (Slade et al. 2016). Another approach has been suggested to include stochastic variation and interactions between individual risk factors to account for the individual trajectories of pain (Svensson and Kumar 2016). While such models may be difficult to prove, they may provide a conceptual framework for understanding the critical clinical question as to why some patients develop chronic TMD muscle pain, while others apparently exposed to similar risk factors do not. In the light of the results of the OPPERA studies, chronic TMD muscle pain presents a multivariate model of risk factors, thus the management resulting from these models must be addressed to all factors.

If clinicians treating chronic TMD muscle pain approach it utilizing univariate models, they will therefore address only one factor in the treatment plan. The controversy of malocclusion and TMD is a good example of univariate thinking with a straight-forward approach to the cure of the problem, such as correction of the malocclusion by means of different techniques such as occlusal

equilibration, occlusal rehabilitation, and orthodontics. Based on the best epidemiological studies, occlusion is a very low risk factor and hence there are other risk factors at play (Svensson and Kumar 2016). This would call for other therapeutic approaches and a suggestion could be that benefit would be obtained from addressing cognitive-behavioral approaches (Svensson and Kumar 2016). There is a wide range of therapies in this domain spanning from information and counselling of patients, to hypnosis and mindfulness. Based on the stochastical model and the many different types of risk and preventive factors, and due respect to the neurobiological mechanisms underlying most orofacial pain conditions, it may be appropriate to also consider pharmacologic therapies. These medications include: TCAs and serotonin-norepinephrine reuptake inhibitors such as amitriptyline (25–150 mg/day), duloxetine (20–120 mg/day) and venlafaxine (150–225 mg/ day); antiepileptics such as pregabalin (150–600 mg/day), gabapentin (900–3600 mg/day), gabapentin ER or gabapentin enacarbil (1200–3600 mg/day); opioids such as tramadol (mainly tramadol ER up to 400 mg daily); oromucosal cannabinoids like cannabis sativa (27 mg/ml delta-9-tetrahydrocannabinol and 25 mg/ml cannabidiol); topical lidocaine (5% lidocaine patches); capsaicin high-concentration patches (8%); and botulinum toxin type A (50–200 units subcutaneously in the painful area).

The efficacy of most medications for alleviation of chronic pain conditions has been modest. Number needed to treat values for most painful conditions are typically in the range of 3-4 or above and the effect size only around 30-40% (Svensson and Kumar 2016). Perhaps with the exception of the triptans for alleviation of acute migraine attacks, few true revolutions in pain pharmacology have been achieved. It seems that a combined approach with cognitive-behavioral approaches, physiotherapy and pharmacology would be a logical suggestion. With this in mind, assuming accurate phenotyping and genotyping of patients, then individualized and poly-target pain management may be feasible. The intensity of the therapy may also vary during the time course due the inherent dynamic nature of the interactions. Conceptually the biopsychosocial pain model and the original RDC/TMD axes I and II approach offered a logical approach to the management of chronic orofacial pain including chronic TMD muscle pain (Fig. 19 A). Most pain management programs are indeed building on this foundation with pharmacology, physiotherapy, self-care programs and more cognitive-behavioral therapy (Fig. 19 B and C). Such combined programs or “packages” of different therapeutic modalities have proven their efficacy to alleviate pain and manage pain, but rarely to completely cure the chronic pain patient (Fig. 19 D). Perhaps the most

important lesson from the stochastic variation model would be that pain management needs to be individualized. In the quest for personalized medicine, we need to consider the individual risk factors and biomarkers. Again conceptually, we may need a third axis in addition to the two axes offered by the RDC/TMD and DC/TMD approach, i.e., an axis which attempts to identify the unique individual biomarker or risk factor. Figure 19 B illustrates such an approach moving from a single axis approach to a three axes approach and the consequences for management (Fig. 19 E). Multimodal pain therapy seems to be more likely to help the chronic orofacial pain patients than single-modality techniques. Clinicians should take the consequence of the current status of orofacial pain and abandon old paradigms, for example over-emphasizing the efficacy of occlusal-oriented treatments. It is not just a future challenge for researchers to continue to unravel the complexity of chronic orofacial pain, but also for clinicians to embrace new pain classifications, concepts and comprehensive assessment of risk factors.

Conclusions and future directions

Masticatory muscle disorders represent the second most common cause of orofacial pain after tooth pain. Differential diagnosis plays an important role since the same symptom (muscular pain) can be the result of different conditions, both local and systemic. The diagnosis is mainly clinical and should be based upon recent diagnostic criteria. A definite instrumental diagnosis is possible for only a few muscular disorders, mainly due to the lack of knowledge related to the pathophysiology of these disorders. The OPPERA study represented the first attempt to open a window into the etiology of temporomandibular disorders and future similar studies are required to fully understand the biological mechanisms determining muscular disorders. Only then can causal therapies be prescribed, and only then can the quality of life of affected patients be improved.