Pain and Headache
Editor: H. Reichmann
Vol. 15

The Puzzle of Orofacial Pain

Integrating Research into Clinical Management

Editors
J.C. Türp
C. Sommer
A. Hugger

KARGER

Pain and Headache

Vol. 15

Series Editor

H. Reichmann, Dresden

The Puzzle of Orofacial Pain

Integrating Research into Clinical Management

Volume Editors

J.C. Türp, Basel
C. Sommer, Würzburg
A. Hugger, Düsseldorf

30 figures, 1 in color, and 19 tables, 2007

KARGER

Basel · Freiburg · Paris · London · New York ·
Bangalore · Bangkok · Singapore · Tokyo · Sydney

Prof. Dr. med. dent. Jens C. Türp
Klinik für Rekonstruktive
Zahnmedizin und Myoarthropathien
Universitätskliniken für Zahnmedizin
Hebelstrasse 3
CH–4056 Basel (Switzerland)

Prof. Dr. med. Claudia Sommer
Neurologische Klinik der Universität
Josef-Schneider-Str. 11
D–97080 Würzburg (Germany)

Prof. Dr. med. dent. Alfons Hugger
Poliklinik für Zahnärztliche Prothetik
Westdeutsche Kieferklinik
Heinrich-Heine-Universität
D–40225 Düsseldorf (Germany)

Library of Congress Cataloging-in-Publication Data

The puzzle of orofacial pain : integrating research into clinical management
/ volume editors, J.C. Türp, C. Sommer, A. Hugger.
p. ; cm. – (Pain and headache, ISSN 0255-3910 ; v. 15)
Includes bibliographical references and indexes.
ISBN 978-3-8055-8270-4 (hard cover : alk. paper)
1. Orofacial pain. 2. Temporomandibular joint–Diseases. I. Türp, Jens Christoph. II. Sommer, C. (Claudia) III. Hugger, Alfons. IV. Series.
[DNLM: 1. Facial Pain. 2. Pain--physiopathology. 3. Temporomandibular Joint Disorders. W1 PA293 v.15 2007 / WE 705 P994 2007]
RC815.P88 2007
617.5′22–dc22
2007006883

Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and Index Medicus.

www.karger.com
Printed in Switzerland on acid-free paper by Reinhardt Druck, Basel
ISSN 0255–3910
ISBN 978–3–8055–8270–4

Contents

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 1–6

Orofacial Pain – A Challenge and Chance (Not Only) for Dentistry

Jens Christoph Türp[a], *Alfons Hugger*[b], *Claudia Sommer*[c]

[a]Klinik für Rekonstruktive Zahnmedizin und Myoarthropathien, Universitätskliniken für Zahnmedizin, Basel, Switzerland; [b]Poliklinik für Zahnärztliche Prothetik, Westdeutsche Kieferklinik, Universitätsklinikum Düsseldorf, Düsseldorf, and [c]Neurologische Klinik der Universität Würzburg, Würzburg, Germany

Abstract

The biomedical concept of care, which is epitomized in daily dental practice, is no longer viable for the diagnosis and management of persistent and chronic (orofacial) pain conditions. The experience of the past 150 years has shown that a mechanistic, narrow approach is likely to produce iatrogenic harm, e.g., unnecessary tooth extractions or temporomandibular joint surgery, and/or to miss clinically important features. Pain distributions outside the trigeminal system as well as concomitant pain-associated psychological and psychosocial findings call for an interdisciplinary (or multidisciplinary) approach. Nonetheless, powerful, yet simple-to-use diagnostic instruments are available for the dentist in order to screen for pain-related features that have traditionally been beyond the dental realm. Although recent pain research has yielded important new insight reaching from the molecular to the clinical level, a number of orofacial pain conditions still remain elusive, among them burning mouth syndrome and persistent idiopathic facial pain. Unfortunately, however, the current state of knowledge is not universally taught in dental education nor is it routinely applied in clinical practice. By increasing the transfer of knowledge gained in pain research for the benefit of the daily clinical work, it will become apparent that the traditional boundaries between dentistry and medicine will vanish.

Pain – particularly chronic pain – continues to destroy the lives of millions of people worldwide. There is no nobler goal than achieving the relief of pain and suffering [1].

Usually, dentists treat what they see, and they see what they treat. Consequently, they are very successful in the treatment of acute pain conditions and many diseases with well-defined etiologies, such as acute pulpal pain.

Problems may arise, however, when this approach is adopted for the management of persistent or chronic orofacial pain. Why is this so?

In contrast to toothache, the causes and underlying mechanisms of most other pain conditions in the orofacial region are still poorly understood [2].[1] Consider for example temporomandibular pain, i.e. pain in the masticatory musculature and/or the temporomandibular joints. For much of the past century, it has been assumed that this musculoskeletal pain condition is exclusively or primarily caused by biomechanical factors such as malalignment of the jaws, premature occlusal contacts or overload of the masticatory muscles and/or temporomandibular joints. However, this still widely held opinion has been largely refuted by current research findings [4, 5]. In addition, a mismatch between the subjective reports of patients and the clinicians' 'objective' findings is frequently encountered: patients report pain in the absence of clinical or image-based findings that could explain the pain perception, as it is typically the case in conditions such as atypical odontalgia, burning mouth syndrome and persistent myofascial pain. An etiology-driven, causal therapy is impossible in most of these conditions.

During the past 150 years, the biomedical concept of etiology and care has dominated western medicine and dentistry. As for pain, it postulates a close correlation between the discharge in peripheral nociceptors due to tissue pathology and the subjective perception and expression of pain. Despite recent research developments, the tendency of dentists to exclusively or predominantly resort to traditional models to explain, diagnose, and treat or manage orofacial pain is still ubiquitous. The well-documented uncertainty of many dental practitioners with regard to the management of patients suffering from orofacial pain is reflected in the abundance of existing diagnostic and treatment modalities, many of which still lack definitive verification of their diagnostic [6, 7] or therapeutic efficacy and effectiveness [8]. Attempts to correct a perceived deviation from a 'biomechanical ideal' and to 'cure at all costs' bear the potential for overdiagnosis and unnecessary interventions. This, in turn, may lead to 'clinical iatrogenesis' [9]. Indeed, a plethora of reports give testimony of iatrogenically induced damage caused by nonsurgical and surgical interventions (e.g. systematic occlusal adjustments for the management or prevention of temporomandibular disorders, unnecessary tooth extractions in

[1] Occasional changes in the official terminology may (often erroneously) suggest that a progress has been achieved in the understanding of certain orofacial pain conditions. Examples for such linguistic modifications are the term 'persistent idiopathic facial pain' that has replaced the formerly used expression 'atypical facial pain' [3], and the term 'temporomandibular joint diseases and disorders' (abbreviated 'TMJD'), which has lately been suggested to replace the still common expression 'temporomandibular disorders' (abbreviated 'TMD' or 'TMDs').

patients suffering from atypical odontalgia or from trigeminal neuralgia, replacement of the articular disk by an alloplastic implant in patients with temporomandibular joint clicking). In a number of cases, the negative effects of irreversible treatments have become a source of suffering that exceeded the original complaints of the patients [10].

Today's medical and dental pain literature is replete with evidence that the biomedical model is inadequate for explaining and controlling not only persistent orofacial pain, but also many other ailments [11]. Instead, a biopsychosocial approach is warranted [12]. Dentists, however, like many physicians, usually do not have adequate education and training in that area. Does this mean that pain-associated psychological and psychosocial issues may be disregarded in the assessment and management of orofacial pain? No, not at all! Reliable and valid screening tools, such as the Graded Chronic Pain Scale [13], are available. These instruments may also be used by dentists in order to assess the presence of psychological and psychosocial impairment in patients suffering from (predominantly long-lasting) pain. The psychological and psychosocial sequelae of persistent/chronic pain [12] as well as the fact that among a considerable part of orofacial pain patients the pain distribution is not limited to the trigeminal system [14, 15] calls for an interdisciplinary (or multidisciplinary) approach. In order to avoid chronicity, early diagnosis and management are crucial [16, 17].

Without doubt, progress in pain research has yielded substantial new insight in recent years, and this has profoundly altered our understanding of various orofacial pain conditions. In temporomandibular pain, for instance, distinct muscle and joint conditions have been recognized. Specific pathomechanisms for muscle pain and joint pain are now known at the molecular level. Furthermore, it has been recognized that the masticatory muscles have many peculiarities as compared to skeletal muscles, which need to be considered for therapeutic planning. The role that inflammatory mediators in the temporomandibular joints play for diagnosis and management has been analyzed in depth so that current knowledge in this area is at least as advanced as in peripheral joint diseases. Furthermore, the influence of hormones, gender, and genes has recently been explored; this will certainly remain a dynamic field of research in the near future.

In spite of all these advances, some orofacial pain entities are still challenging and may merely be identified by clinical description. Burning mouth syndrome is one such example of a condition that, at present, we cannot fully explain pathophysiologically. Another example is so-called persistent idiopathic facial pain, a diagnostic umbrella term that becomes progressively smaller, as exclusionary factors are identified. However, in particular for these elusive pain conditions, it is important to adhere to strict clinical observation.

Only if the afflicted patients are thoroughly investigated, considering all relevant somatic and psychosocial aspects, may we achieve progress in the search for the pathophysiological background of the disorder and thus offer better therapeutic options.

'The deep psychological and physiologic significance of the face and mouth, the highly subjective nature of the individual's reaction to pain, and the anatomic complexity that leads to such a variety of possible causes of facial pain, all indicate the need for (…) a sensitive and individualized approach to the management of facial pain.' This statement from Laszlo Schwartz and Charles M. Chayes [18] nicely reflects the peculiarities associated with pain in the orofacial region. Today, it is still as true as it was in 1968, when it was published in the authors' textbook *Facial Pain and Mandibular Dysfunction*. Currently, obvious differences exist between medicine and dentistry with regard to the diagnosis and management of persistent/chronic pain conditions. It appears that this discrepancy is, at least in part, related to shortcomings in dental education. Curriculum guidelines for under- and postgraduate programs in orofacial pain and temporomandibular disorders have been proposed by various organizations, including the International Association for the Study of Pain [19] and the European Academy of Craniomandibular Disorders [20]. In addition, excellent textbooks and journals dedicated to orofacial pain have been published. Yet, these activities do not appear to have had a profound effect on dental education and patient management. Although there continues to be a substantial public need and demand for services in the area of orofacial pain, most dental schools have not incorporated mandatory graduate courses and programs in their curriculum. Moreover, if this topic is addressed, it is not always taught according to the current state of the art [21]. Unless the mechanistic approach still governing in many schools and practices is abandoned, the 'dilemma of scientific knowledge versus clinical management' [22] is likely to continue. Hence, improvement of the knowledge transfer from current best research into the clinical practice remains one of the most important tasks in dentistry and medicine [23].

While our profession gradually recognizes the need for a shift from authority-driven and opinion-based dentistry to evidence-based dental health care, we observe major advances in the understanding of the neurobiology of pain and the underlying molecular mechanisms. As a consequence, traditional boundaries between different fields of health care are becoming more and more obsolete. Orofacial pain, with its strong ties to all dental and many medical disciplines (as well as clinical psychology), offers the unique opportunity to link clinical dentistry closer with medicine and the basic sciences. Inter- and multidisciplinary efforts are required to foster an advanced understanding of the diverse orofacial pain conditions and, by doing so, to improve patient care.

The present textbook aims at contributing to a better understanding of the puzzle of (orofacial) pain. The editors would like to express their sincere gratitude to all authors – world-renowned researchers and clinicians – for the time and effort to deliver state-of-the-art chapters. We are grateful for their contributions.

References

1 Melzack R: Foreword; in McMahon SB, Koltzenburg M (eds): Wall and Melzack's Textbook of Pain, ed 5. Philadelphia, Elsevier, 2006, pp xi.
2 Sessle BJ: Factors bearing on causes and management of orofacial pain. J Orofac Pain 2006; 20:189.
3 Headache Classification Subcommittee of the International Headache Society: The International Classification of Headache Disorders, 2nd edition. Cephalalgia 2004;24(suppl 1):9–160.
4 Gesch D, Bernhardt O, Alte D, Kocher T, John U, Hensel E: 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 2004;65:88–103.
5 Gesch D, Bernhardt O, Mack F, John U, Kocher T, Alte D: Association of malocclusion and functional occlusion with subjective symptoms of TMD in adults: results of the Study of Health in Pomerania (SHIP). Angle Orthod 2005;75:183–190.
6 Baba K, Tsukiyama Y, Yamazaki M, Clark GT: A review of temporomandibular disorder diagnostic techniques. J Prosthet Dent 2001;86:184–194.
7 Farella M, Michelotti A, Pellegrino G, Giani U, Martina R: Interexaminer reliability and validity for diagnosis of temporomandibular disorders of visual leg measurements used in dental kinesiology. J Orofac Pain 2005;19:285–290.
8 Koh H, Robinson PG: Occlusal adjustment for treating and preventing temporomandibular joint disorders. Cochrane Database Syst Rev 2003;1:CD003812.
9 Illich I: Medical Nemesis: The Expropriation of Health. New York, Pantheon Books, 1976.
10 Ostermann AC, Dowdy JD, Lindemann S, Türp JC, Swales J: Patterns in self-reported illness experiences: letters to a TMJ support group. Lang Commun 1999;19:127–147.
11 Engel GL: From biomedical to biopsychosocial. 1. Being scientific in the human domain. Psychother Psychosom 1997;66:57–62.
12 Suvinen TI, Reade PC, Kemppainen P, Könönen M, Dworkin SF: 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 2005;9: 613–633.
13 Von Korff M, Ormel J, Keefe FJ, Dworkin SF: Grading the severity of chronic pain. Pain 1992;50: 133–149.
14 Türp JC, Kowalski CJ, O'Leary N, Stohler CS: Pain maps from facial pain patients indicate a broad pain geography. J Dent Res 1998;77:1465–1472.
15 Sipilä K, Ylöstalo PV, Joukamaa M, Knuuttila ML: Comorbidity between facial pain, widespread pain, and depressive symptoms in young adults. J Orofac Pain 2006;20:24–30.
16 Greene CS: Managing TMD patients: initial therapy is the key. J Am Dent Assoc 1992;123:43–45.
17 Palla S: A need to redefine chronic pain? J Orofac Pain 2006;20:265–266.
18 Schwartz L, Chayes CM: Facial Pain and Mandibular Dysfunction. Philadelphia, Saunders, 1968, p 5.
19 Charlton JE (ed): Core Curriculum for Professional Education in Pain, ed 3. Seattle, IASP Press, 2005, pp 191–192.
20 Nilner M, Steenks M, De Boever J, Ciancaglini R, Könönen M, Orthlieb JD: Guidelines for curriculum of undergraduate and postgraduate education in orofacial pain and temporomandibular disorders in Europe. J Orofac Pain 2003;17:359–362.

21 Klasser GD, Greene CS: Predoctoral teaching of temporomandibular disorders: a survey of U.S. and Canadian dental schools. J Am Dent Assoc 2007;138:231–237.
22 Mohl ND, Ohrbach R: The dilemma of scientific knowledge versus clinical management of temporomandibular disorders. J Prosthet Dent 1992;67:113–120.
23 Türp JC: Why all the quarreling over evidence-based dentistry? Quintessence Int 2007;38:175.

Prof. Dr. med. dent. Jens Christoph Türp
Klinik für Rekonstruktive Zahnmedizin und Myoarthropathien
Universitätskliniken für Zahnmedizin, Hebelstrasse 3
CH–4056 Basel (Switzerland)
Tel. +41 61 267 2632, Fax +41 61 267 2660, E-Mail jens.tuerp@unibas.ch

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 7–17

Characteristics of Muscle Nociception

Siegfried Mense

Institut für Anatomie und Zellbiologie III, Universität Heidelberg, Heidelberg, Germany

Abstract

Nociceptive nerve endings in muscles are equipped with a multitude of receptor molecules for endogenous pain-producing and sensitizing agents. Particularly interesting for muscle pain are (1) purinergic receptors (e.g. P2X3) activated by adenosine triphosphate (ATP), (2) transient receptor potential vanilloid receptors of subtype 1 (formerly called VR1) activated by protons and heat and (3) tyrosine kinase receptors A activated by nerve growth factor (NGF). ATP is considered a general pain signal, because all cells contain ATP and release it when they are damaged. A low tissue pH is characteristic of many pathological conditions in muscle, such as ischemia and tonic contractions; NGF is released in ischemic and inflamed muscle and has the exceptional property of exciting nociceptive nerve endings exclusively. In the central nervous system, input from muscle nociceptors induces marked neuroplastic changes that result in hyperexcitability and hyperactivity of nociceptive central neurons. This central sensitization is assumed to be responsible for the spontaneous pain and hyperalgesia of patients and is important for the transition from acute to chronic muscle pain. The final step of the transition to chronic pain is characterized by structural changes in neurons and glial cells. A patient with morphological alterations of the nociceptive system is difficult to treat, because the changes need time to normalize.

Muscle pain differs in several aspects from cutaneous and visceral pain. Subjectively, muscle pain is difficult to localize and – in contrast to cutaneous pain – is referred to other deep somatic tissues (fascia, muscle, joints) [for a review, see 1]. Activation of muscle receptors does not elicit flexor reflexes, and muscle pain has a special relay in the mesencephalon [2]. With regard to orofacial pain, it is important to note that the nociceptive wiring in the brainstem differs from that in the spinal cord. For instance, following noxious stimulation of facial skin there is no ipsilateral flexor and contralateral extensor reflex of the jaw-closing muscles.

This chapter deals with peripheral and central nervous mechanisms of muscle pain as observed in experimental animals (mainly rats). To what extent these data can be transferred to patients is an open question, but the experience from many studies has shown that the basic pain mechanisms (particularly at the primary afferent and spinal level) in experimental animals and patients are similar.

Peripheral Mechanisms

Morphologically, a muscle nociceptor is a free nerve ending that is connected to the central nervous system via nonmyelinated (group IV) or thinly myelinated (group III) afferent fibers. Most data in the literature were obtained from endings with group IV afferent fibers that have a mean conduction velocity of approximately 1 m/s.

Muscle nociceptors are activated by noxious (tissue-threatening, subjectively painful) or potentially noxious stimuli. They have a high mechanical stimulation threshold and are not excited by physiological movements or muscle stretch. In pathologically altered muscle tissue (e.g. following trauma or in inflamed muscle), nociceptors are sensitized and lower their stimulation threshold into the innocuous range. This means that under pathological conditions, muscle nociceptors may be activated by everyday stimuli such as weak pressure or movements. This is the reason for the pain perceived during movement of a damaged muscle [for a review, see 3].

For a long time, muscle nociceptors have been known to be activated by inflammatory substances such as bradykinin, serotonin and prostaglandins of the E type [4, 5]. Receptor molecules for these endogenous pain-producing and sensitizing agents are present in the membrane of nociceptive nerve endings [6]. When tested with various combinations of inflammatory substances, many group IV endings from muscle respond only to some of the agents. A possible reason for this special chemical sensitivity is a particular combination of receptor molecules in the membrane of the nociceptive endings. For instance, nociceptors that are excited by noxious (tissue-threatening, subjectively painful) mechanical stimuli are assumed to possess receptor molecules of the ankyrin-repeat transient receptor potential receptor family, whereas receptive endings that are activated by light mechanical stimuli are thought to be equipped with transient receptor potential or degenerin/epithelial Na^+ channels [7].

One type of muscle nociceptor found by our group was particularly sensitive to ischemic contractions. It did not respond to contractions with the muscle circulation intact, but when the contractions were induced after occlusion of the muscle artery, the nociceptor was activated [8]. Possibly, these are the receptive

endings that elicit the pain of intermittent claudication and maybe also that of tonic contractions. One receptor molecule discussed in this regard is the acid-sensing ion channel 3 (ASIC3 [9]). The pain of those patients with tension-type headache who show increased electromyographic activity in their cranial muscles may originate in this subtype of muscle nociceptor.

Prostaglandin E_2 and serotonin, respectively, are known to sensitize muscle free nerve endings to bradykinin and mechanical stimuli. The pain elicited in volunteers by injection of a combination of bradykinin and serotonin into the temporal muscle is likewise stronger than that caused by each stimulant alone. These interactions are of practical significance because the substances are released together in damaged tissue.

This chemical sensitization of nociceptors is assumed to be the peripheral neurophysiological basis of tenderness (allodynia) and hyperalgesia of a damaged muscle. The sensitization of peripheral nociceptors has to be differentiated from central sensitization (see below). The tenderness and hyperalgesia of patients often have both a peripheral and a central nervous component.

Recently, other stimulants have attracted much interest, namely adenosine triphosphate (ATP), protons (drop in tissue pH), inflammatory cytokines (e.g. interleukins) and neurotrophins (e.g. nerve growth factor, NGF). Receptor molecules for these substances have been found in the dorsal root ganglion cells of muscle afferent fibers, particularly in cells of small size (fig. 1).

ATP acts on the purinergic receptor P2X3 [10]. Purinergic receptors are activated by any tissue damage because all cells of the body contain ATP. Therefore, ATP has been considered the general signal for tissue lesions by some investigators. Animal experiments have shown that muscle nociceptors respond to ATP in concentrations that are present in muscle cells [11]. Intramuscular injections of 36 mM solutions of ATP have been reported to cause strong pain in humans [12].

Protons open the various types of ASICs at different degrees of tissue acidity and also activate transient receptor potential vanilloid receptor of subtype 1 (TRPV1) [13], which is also sensitive to heat. ASICs and TRPV1 are of particular interest for muscle pain, because in muscle tissue there is a drop in tissue pH under many conditions, such as exhausting work, ischemia and inflammation. Inflamed or ischemic tissue is known to have a pH of 5–6, and in animal experiments of the author's group, these degrees of acidity activated muscle group IV endings [14]. TRPV1 receptors of cutaneous nociceptors have been shown to be activated by the body temperatures if the tissue pH is low (e.g. in inflammation or ischemia [15]). Thus, body temperature may become a stimulus for nociceptors in damaged tissue. The proton-sensitive nociceptors may be of importance for the induction of chronic muscle pain: there is evidence in the literature indicating that repeated intramuscular administration of acidic

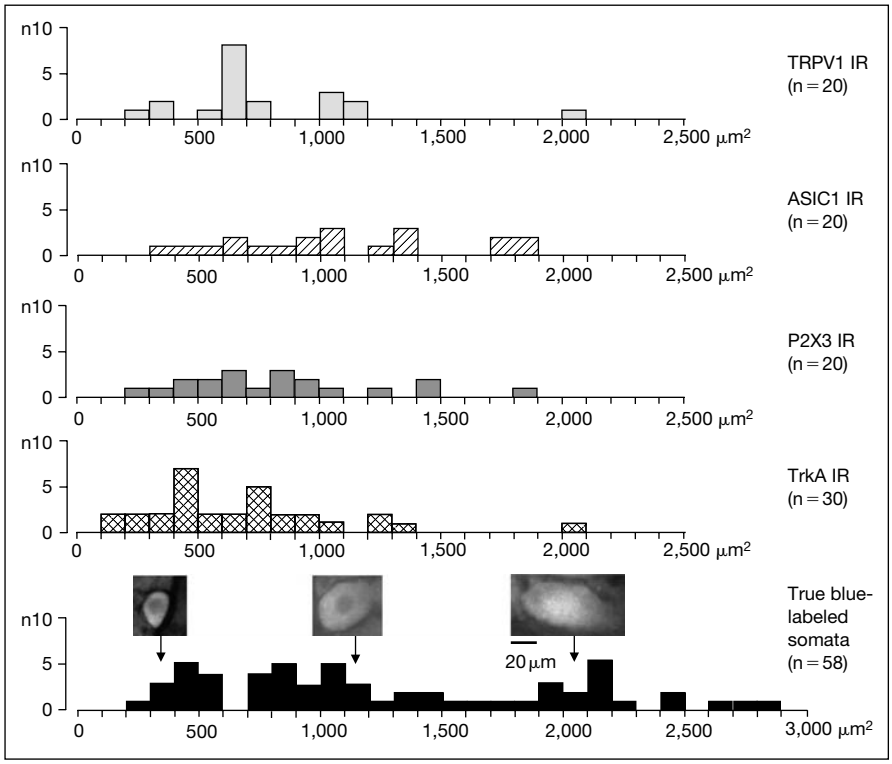

Fig. 1. Expression of receptor molecules in L_5 dorsal root ganglion cells that supplied receptive endings in the rat gastrocnemius-soleus muscle. The cells were retrogradely labeled with injections of True blue into the muscle. The lowermost panel shows the size distribution of 58 retrogradely labeled cells to demonstrate the size spectrum of somata in the ganglion. In the other panels, retrogradely labeled cells are shown that exhibited immunoreactivity (IR) for the TRPV1, ASIC1, P2X3 or tyrosine kinase A (TrkA) receptor molecules. Note that immunoreactivity for the receptor molecules was present mainly in small cells, many of which are likely to have unmyelinated afferent fibers.

solutions results in long-lasting hyperalgesia [16]. It is tempting to speculate that the pain associated with bruxism (jaw clenching, tooth grinding) as well as tension-type headache could be mediated by nociceptors with ASICs and TRPV1, respectively, because these conditions are likely to result in muscle ischemia and low tissue pH.

In experiments by the author's group, ATP and acidic solutions were effective stimulants for muscle receptors with group IV afferent fibers in the rat. Sixty to 80% of the tested receptors were excited by intramuscular injections of ATP (concentration 7.6 mM) or by a pH of 6 [11, 14]. However, these chemical

stimuli were not specific for muscle nociceptors, because also low-threshold mechanosensitive (presumably nonnociceptive) group IV endings were excited.

Among the neurotrophins, NGF with its receptor tyrosine kinase receptor A is of particular interest for muscle pain. When injected intramuscularly at (patho)physiological concentrations in anesthetized animals, it excited 40% of the group IV muscle afferent units tested. NGF differed from all other stimulants tested so far in that it excited exclusively high-threshold mechanosensitive (presumable nociceptive) group IV endings [17]. NGF may also be of importance for chronic muscle pain. Intramuscular injections in humans showed that at a certain concentration (0.8 μM) NGF does not elicit pain upon injection, but is followed by a marked hyperalgesia of the injected muscle for more than 1 week [18]. Awake rats exhibited the same combination of lack of pain reaction to NGF injection followed by hyperalgesia of the injected muscle [U. Hoheisel and S. Mense, unpubl. result]. The absence of pain-related behavior during intramuscular injection in rats is difficult to explain, given the relatively marked excitation of muscle nociceptors. Recent experimental evidence from our group [U. Hoheisel and S. Mense, unpubl. result] indicates that NGF causes mainly subthreshold potentials in dorsal horn neurons, which are not transmitted to higher centers and therefore do not cause pain.

In chronically inflamed muscle of rats, group IV afferent units exhibit a significant increase in resting activity (possibly causing spontaneous dysesthesias and pain in patients) as well as a reduced mechanical stimulation threshold (possibly leading to tenderness). Contrary to expectations, group IV endings in inflamed muscle did not exhibit increased but decreased sensitivity to ATP, pH and NGF. Effects of protons on endings in inflamed muscle are shown in figure 2. A solution of pH 6 excited significantly fewer receptive endings in inflamed than in intact muscle. We conclude from this finding that the pH in the inflamed muscle must have been close to 6, and therefore the injection of a solution with the same pH was not a stimulus for the receptors.

Mechanisms of Muscle Pain at the Spinal Level

Myositis-Induced Neuroplastic Changes in the Spinal Dorsal Horn

Input from peripheral nociceptors to the spinal cord or brainstem is known to lead to changes in function, and later connectivity, of sensory dorsal horn neurons and neurons in the trigeminal nucleus caudalis, respectively. Input from nociceptors in muscle is more effective in this regard than input from cutaneous ones [19]. The lesion-induced neuroplastic changes in the spinal dorsal horn are so marked that the term ‘functional reorganization of the dorsal horn’ has been used to describe these changes. In experiments on anesthetized rats, such

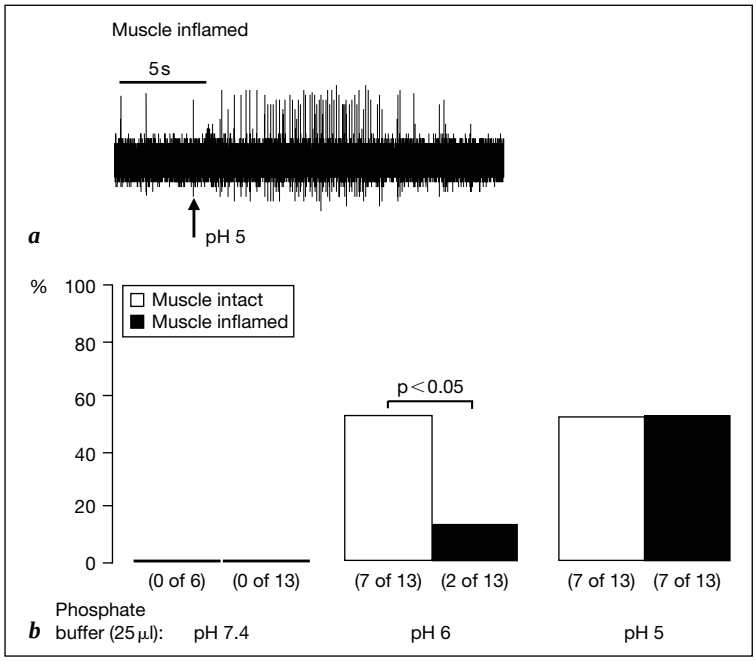

Fig. 2. Comparison of the effects of acidic solutions on group IV receptors in rats with chronically inflamed and intact muscle. ***a*** Original (digitized) registration of the discharges of a single muscle group IV fiber in response to intramuscular injection of phosphate buffer solution (pH 5) close to the receptive ending. ***b*** Proportion of group IV endings excited by solutions of various pH in intact and inflamed muscle. pH 7.4, i.e. neutral pH, had no excitatory action. pH 6 was less effective in inflamed than in intact muscle, probably because the pH of the inflamed muscle was close to pH 6. pH 5 was equally effective in inflamed and intact muscle, probably because this pH was clearly below the tissue pH under both conditions and, therefore, constituted a stimulus for group IV endings.

changes occurred within a few hours after an experimental muscle lesion. The most conspicuous spinal effect of such a lesion was an expansion of the spinal input region of the muscle nerve, i.e. the population of dorsal horn neurons that responded to electrical stimulation of the gastrocnemius-soleus muscle nerve grew larger [20]. In other words, the excitation of dorsal horn neurons elicited by afferent fibers from muscle spread to adjacent neuron populations. This central sensitization is assumed to be one of the first steps in the transition from acute to chronic muscle pain. The most likely explanation for the expansion of the muscle-induced excitation is that existing – but ineffective – synaptic connections between muscle afferents and dorsal horn neurons become more effective in animals with myositis. This leads to hyperexcitability of the neurons. In

patients, this hyperexcitability is likely to elicit more pain during noxious stimulation (i.e. hyperalgesia), whereas the expansion of the muscle-induced excitation in the dorsal horn may be the reason for the spread and referral of muscle pain (see below).

At the molecular level, the lesion-induced central sensitization includes many processes. One is that the nociceptive afferent activity releases glutamate (the common nociceptive transmitter) together with substance P from presynaptic boutons of the afferent fibers. The combined action of glutamate and substance P opens postsynaptic N-methyl-D-aspartate channels through which Ca^{2+} ions enter the dorsal horn neuron. Ca^{2+} ions are second messengers that activate a multitude of intracellular enzymes. Important enzymes in this regard are protein kinases that phosphorylate existing ion channels in the membrane of the postsynaptic neuron [21]. Phosphorylated ion channels are more effective, i.e. they are better permeable for ions. In the long run, also the gene expression in the nucleus of the postsynaptic neuron changes, which leads to a de novo synthesis of ion channel proteins. The result of these processes is a sensitized neuron that is hyperexcitable by noxious and innocuous stimuli.

Neurotransmitters and Neuropeptides Involved in Myositis-Induced Central Sensitization

The finding that intrathecal administration of antagonists to substance P and N-methyl-D-aspartate receptors prevented the myositis-induced expansion of the target area suggests that substance P acting on neurokinin 1 receptors and glutamate acting on N-methyl-D-aspartate receptors are involved in these changes [22]. In contrast, the background or resting activity of the same dorsal horn neurons appears to depend strongly on the release of nitric oxide (NO) in the spinal cord [23]. A block of the NO-synthesizing enzyme NO synthase led to a significant increase in background activity. These data indicate that NO is released tonically in the dorsal horn and inhibits the background discharge of nociceptive neurons. The background activity is of clinical importance because it is assumed to be responsible for spontaneous pain and dysesthesia in patients. The effects of NO are controversial in the literature, with some regarding it as a pronociceptive and some as an antinociceptive agent. A recent report showed that NO and cGMP (cyclic guanosine monophospate, a second messenger that needs NO for synthesis) have different actions at the spinal and supraspinal level, which might be a possible explanation for some of the discrepancies in the literature. At the supraspinal level, NO and cGMP were found to be pronociceptive, and at the spinal level, antinociceptive [24] (fig. 3). Therefore, the effects of agents that interfere with the synthesis of NO or cGMP depend on the site of action. Interestingly, some of the patients taking sildenafil (a compound that increases the cGMP level) complain of myalgias.

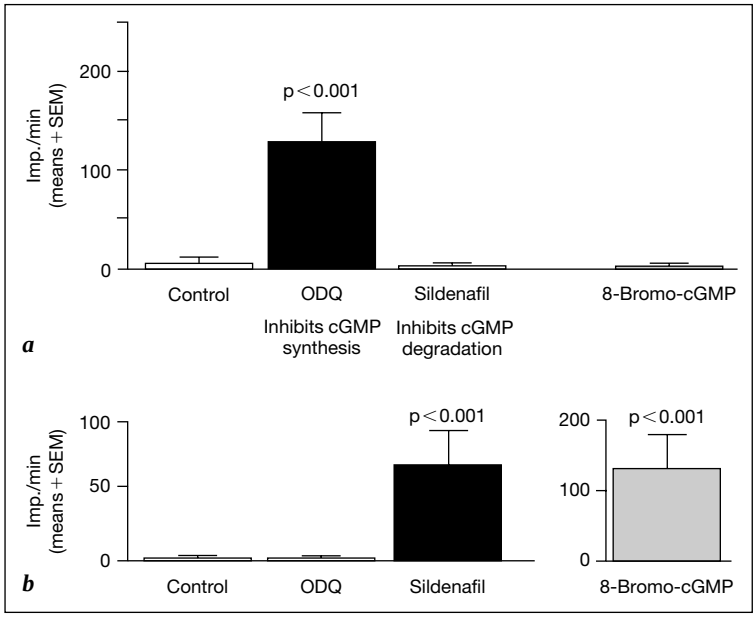

Fig. 3. Effects of manipulating the spinal and supraspinal cGMP level on dorsal horn neurons in the segments L_4 and L_5. Imp. = Impulses. ***a*** Local spinal administration of the agents by superfusion of the spinal cord, resulting in a thin film of the substances around the cord. ODQ [1H-(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one] is a blocker of the guanylyl cyclase and lowers the cGMP level by reducing the synthesis of cGMP; it activated the neurons. Sildenafil, a blocker of the cGMP-degrading enzyme phosphodiesterase 5, increases the cGMP level; it had no recognizable effect on the neurons. Superfusion of the spinal cord with 8-bromo-cGMP, a membrane-permeable cGMP analogue which directly increases the cGMP level, was likewise without effect. ***b*** Injection of the substances at the supraspinal level (intracerebroventricular injection into the third cerebral ventricle) caused opposite effects: now ODQ did not influence the neurons, whereas sildenafil and 8-bromo-cGMP were excitatory. The effects on lumbar neurons elicited by intracerebroventricular injection were probably mediated by descending pain-modulating pathways.

The results obtained with intramuscular injections of NGF, namely the surprising combination of lack of pain upon injection with marked hyperalgesia afterwards, raises the question how a stimulus that does not elicit subjective sensations can induce central sensitization. What is even more puzzling is the fact that NGF excites a relatively high proportion of muscle nociceptors but this peripheral activity does not cause subjective sensations. Given that in spinal dorsal horn cells NGF elicits mainly subthreshold potentials and only few action potentials, a possible explanation is that the subthreshold potentials are not transmitted to higher nociceptive centers but induce sensitization in dorsal

horn cells. If this interpretation is correct, everyday muscle lesions may elicit subthreshold potentials in spinal neurons which are not felt subjectively but may cause central sensitization.

Mechanism of Referral of Muscle Pain

The expansion of the spinal target area of muscle afferent fibers in animals with a muscle lesion may be the mechanism that underlies the spread and referral of pain which is common in patients with myofascial trigger points and other muscle disorders. The following chain of events may occur in pain referral: when a muscle is damaged, the patient first perceives local pain at the site of the lesion. Local pain is mediated by those spinal neurons that have effective synapses with the nociceptors of the painful muscle. If the nociceptive muscle input is strong or long-lasting, central sensitization in the dorsal horn is induced, which opens silent synapses and leads to an expansion of the target area of the nociceptors of the damaged muscle in the spinal cord or brainstem. When the expansion of the lesion-induced excitation reaches sensory neurons that supply body regions remote from the damaged muscle, the patient will feel pain in that area. In the area of pain referral, no nociceptor is active and the tissue is normal. This way, trigger points in the temporalis muscle can induce pain in the teeth of the maxilla when the trigger-point-induced central excitation spreads to sensory neurons that supply the teeth [25].

Transition from Acute to Chronic Muscle Pain

In most cases, the functional changes in the spinal cord and brainstem will outlast the peripheral lesion. Neuroplastic changes such as the opening of synapses are one of the first steps in the transition from acute to chronic pain because they can persist for long periods of time. Another step in the direction of chronic pain are lesion-induced metabolic changes in sensory spinal neurons, for instance in those that synthesize NO or cGMP.

The last step in the transition from acute to chronic muscle pain is characterized by morphological changes in the circuitry of the spinal dorsal horn. The changes include sprouting of the spinal terminals of afferent fibers and new formation and broadening of synaptic contacts. The structural alterations may last for years or become permanent, because even normal input can maintain the alterations if the nociceptive neurons are hyperexcitable.

Recent data indicate that also glial cells may be involved in central sensitization by releasing inflammatory cytokines and chemokines, i.e. the glial cells mediate a so-called neuroinflammation [26]. This mechanism appears to occur also during muscle lesions, as chronic nociceptive input from muscle has been shown to cause metabolic and morphological changes in astrocytes [27]. These changes consisted in an increase in the expression of the astrocyte-specific

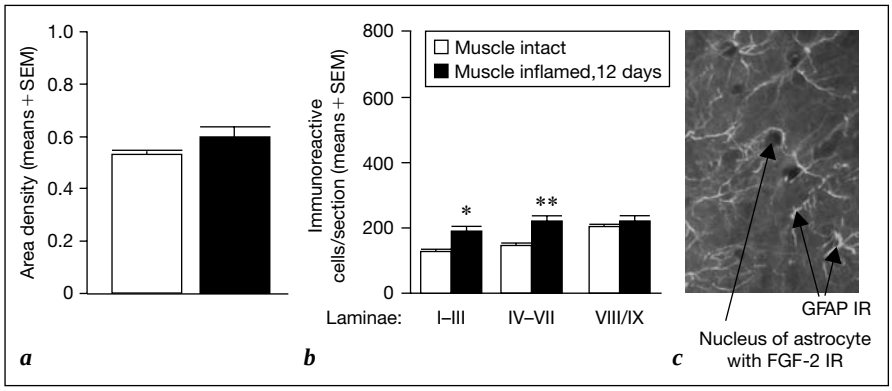

Fig. 4. Effects of a chronic myositis on the metabolic activity of astrocytes. ***a*** The numerical area density of the immunoreactivity to glial fibrillary acidic protein (GFAP) in astrocytes was higher in myositis animals than in rats with intact muscle. This finding indicates that the input from the inflamed muscle induced a higher synthesis rate of GFAP in astrocytes (the number of astrocytes per section area was unchanged). ***b, c*** Effects of a chronic myositis on the synthesis of fibroblast growth factor 2 (FGF-2) in astrocytes. ***c*** Double labeling of astrocytes with antibodies to GFAP (white) and FGF-2 (dark). The spider-like white structures are GFAP-filled processes of astrocytes, the dark areas nuclei of astrocytes synthesizing FGF-2. IR = Immunoreactivity. ***b*** The proportion of astrocytes exhibiting FGF-2 immunoreactivity in their nuclei was higher in myositis animals, but only in the dorsal horn and substantia intermedia (laminae I–VII). These are regions where the nociceptive input from the inflamed muscle terminates. *$p < 0.01$, **$p < 0.001$.

protein glial fibrillary acidic protein and an increase in the proportion of the astrocytes synthesizing fibroblast growth factor 2 (fig. 4). Altogether, the functional, metabolic and structural changes in the nociceptive central network form the ‘pain memory’ which is difficult to erase with therapeutic interventions. Therefore, an important principle in the treatment of muscle pain is to abolish the nociceptive input from the muscle to the spinal cord as early as possible to prevent lesion-induced central nervous alterations.

References

1 Mense S, Simons DG: Muscle Pain: Understanding Its Nature, Diagnosis, and Treatment. Baltimore, Lippincott, Williams & Wilkins, 2001.

2 Keay KA, Bandler R: Deep and superficial noxious stimulation increases Fos-like immunoreactivity in different regions of the midbrain periaqueductal grey of the rat. Neurosci Lett 1993;154:23–26.

3 Mense S: The pathogenesis of muscle pain. Curr Pain Headache Rep 2003;7:419–425.

4 Kumazawa T, Mizumura K: Thin-fiber receptors responding to mechanical, chemical, and thermal stimulation in the skeletal muscle of the dog. J Physiol 1977;273:179–194.

5 Mense S, Meyer H: Different types of slowly conducting afferent units in cat skeletal muscle and tendon. J Physiol 1985;363:403–417.
6 McCleskey EW, Gold MS: Ion channels of nociception. Annu Rev Physiol 1999;61:835–856.
7 Goodman MB, Lumpkin EA, Ricci A, Tracey WD, Kernan M, Nicolson T: Molecules and mechanisms of mechanotransduction. J Neurosci 2004;24:9220–9222.
8 Mense S, Stahnke M: Responses in muscle afferent fibres of slow conduction velocity to contractions and ischaemia in the cat. J Physiol 1983;342:383–397.
9 Immke DC, McCleskey EW: Protons open acid-sensing ion channels by catalyzing relief of Ca^{2+} blockade. Neuron 2003;9:75–84.
10 Burnstock G: P2X receptors in sensory neurones. Br J Anaesth 2000;84:476–488.
11 Reinöhl J, Hoheisel U, Unger T, Mense S: Adenosine triphosphate as a stimulant for nociceptive and non-nociceptive muscle group IV receptors in rat. Neurosci Lett 2003;338:25–28.
12 Mörk H, Ashina M, Bendtson L, Olesen J, Jensen R: Experimental muscle pain and tenderness following infusion of endogenous substances in humans. Eur J Pain 2003;7:145–153.
13 Caterina MJ, David J: Sense and specificity: a molecular identity for nociceptors. Curr Opin Neurobiol 1999;9:525–530.
14 Hoheisel U, Reinöhl J, Unger T, Mense S: Acidic pH and capsaicin activate mechanosensitive group IV muscle receptors in the rat. Pain 2004;110:149–157.
15 Reeh PW, Kress M: Molecular physiology of proton transduction in nociceptors. Curr Opin Pharmacol 2001;1:45–51.
16 Sluka KA, Kalra A, Moore SA: Unilateral intramuscular injections of acidic saline produce a bilateral long-lasting hyperalgesia. Muscle Nerve 2001;24:37–46.
17 Hoheisel U, Unger T, Mense S: Excitatory and modulatory effects of inflammatory cytokines and neurotrophins on mechanosensitive group IV muscle afferents in the rat. Pain 2005;114:158–176.
18 Svensson P, Cairns BE, Wang K, Arendt-Nielsen L: Injection of nerve growth factor into human masseter muscle evokes long-lasting mechanical allodynia and hyperalgesia. Pain 2003;104: 241–247.
19 Wall PD, Woolf CJ: Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. J Physiol 1984;356:443–458.
20 Hoheisel U, Koch K, Mense S: Functional reorganization in the rat dorsal horn during an experimental myositis. Pain 1994;59:111–118.
21 Millan MJ: The induction of pain: an integrative review. Prog Neurobiol 1999;57:1–164.
22 Hoheisel U, Sander B, Mense S: Myositis-induced functional reorganization of the rat dorsal horn: effects of spinal superfusion with antagonists to neurokinin and glutamate receptors. Pain 1997;69:219–230.
23 Hoheisel U, Unger T, Mense S: A block of the nitric oxide synthesis leads to increased background activity predominantly in nociceptive dorsal horn neurons in the rat. Pain 2000;88:249–257.
24 Hoheisel U, Unger T, Mense S: The possible role of the NO-cGMP pathway in nociception: Different spinal and supraspinal action of enzyme blockers on rat dorsal horn neurones. Pain 2005;117:358–367.
25 Simons DG, Travell JG, Simons LS: Travell and Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual, ed 4. Baltimore, Williams & Wilkins, 1999, vol 1: Upper half of body.
26 Watkins LR, Maier SF: Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. Physiol Rev 2002;82:981–1011.
27 Tenschert S, Reinert A, Hoheisel U, Mense S: Effects of a chronic myositis on structural and functional features of spinal astrocytes in the rat. Neurosci Lett 2004;361:196–199.

Prof. Dr. Siegfried Mense
Institut für Anatomie und Zellbiologie III, Universität Heidelberg
Im Neuenheimer Feld 307
DE–69120 Heidelberg (Germany)
Tel. +49 6221 54 41 93, Fax +49 6221 54 60 71, E-Mail mense@urz.uni-heidelberg.de

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 18–27

Nociceptors of the Joint with Particular Reference to Silent Nociceptors

Hans-Georg Schaible

Institut für Physiologie I, Lehrstuhl für Neurophysiologie, Universität Jena, Jena, Germany

Abstract

This chapter summarizes recent research on mechanisms by which diseased joints become painful. Joints are supplied with sensory Aβ, Aδ and C fibers. While the vast majority of Aβ fibers have their mechanical threshold in the innocuous range, large proportions of Aδ and C fibers have high thresholds and are only activated by noxious mechanical stimuli applied to the joint. In addition, the joint nerves contain silent nociceptors which are mechanoinsensitive when the joint is normal. These units are neither activated by local mechanical stimulation of the joint nor by innocuous and noxious joint movements. However, they show some chemosensitivity. During development of inflammation in the joint, articular afferents show increased mechanosensitivity. While low-threshold fibers show stronger responses to innocuous and noxious stimuli, high-threshold fibers show a reduction of their mechanical threshold and are then activated by normally innocuous stimuli. In addition, numerous silent nociceptors become mechanosensitive. At this stage, a receptive field can be localized in the joint, and formerly silent nociceptors begin to respond to joint movements. Present evidence suggests that the induction of mechanosensitivity results from the action of inflammatory mediators on these neurons. The recruitment of these fibers for sensory processing under inflammatory conditions is thought to be an important mechanism for the induction of inflammation-evoked spinal hyperexcitability.

Perceptions from the Joint

Sensory information from the joint influences the motor system and it is involved in the sense of movement and position. In daily life, however, we are not aware of these sensory functions. The only perception that is unequivocally attributed to the joint is pain. In a normal joint, pain is commonly elicited by twisting or hitting the joint. This rarely applies to the temporomandibular joints

(TMJ). Of great clinical relevance is the joint pain after injury, during inflammation and in the course of joint degeneration. Injury and inflammation of the joint are characterized by hyperalgesia and persistent pain at rest, which is usually dull and badly localized [1–4]. Noxious stimuli cause stronger pain than normal, and pain is even evoked by mechanical stimuli whose intensity does not normally elicit pain, i.e. movements in the working range and gentle pressure, e.g. during palpation. Pain during degenerative osteoarthritis shows similarities *and* differences to arthritic pain. As with arthritis, pain may increase when the joint is being loaded [5]. However, pain may also be reduced during walking and may be particularly severe during rest at night when the joint is immobile.

Experimental invasive sensory testing in conscious humans revealed that pain in the normal joint can be elicited when noxious mechanical and chemical stimuli are applied to the fibrous structures, such as ligaments and fibrous capsule [2]. No pain is elicited by stimulation of cartilage, and stimulation of normal synovial tissue rarely evokes pain. Stimulation of fibrous structures with innocuous mechanical stimuli can evoke pressure sensations [2].

Innervation of the Joint

Big joints such as the knee joint are supplied by branches descending from main nerve trunks or their muscular, cutaneous and periosteal branches. The TMJ is innervated mainly by branches from the trigeminal nerve. A typical joint nerve contains thick myelinated Aβ (group II), thinly myelinated Aδ (group III) and a high proportion (approx. 80%) of unmyelinated C (group IV) fibers. The latter are either sensory afferents or sympathetic efferents (each approx. 50%) [6].

Articular Aβ fibers terminate as corpuscular endings of the Ruffini, Golgi and Pacini type in the fibrous capsule, articular ligaments, menisci and adjacent periosteum [7]. Articular Aδ and C fibers terminate as noncorpuscular or free nerve endings in the fibrous capsule, adipose tissue, ligaments, menisci and the periosteum. Using staining for nerve fibers and neuropeptides, endings were also identified in the synovial layer. The cartilage is not innervated [6]. Typical free nerve endings in the joint are ensheathed by Schwann cells, and only some sites are not covered, suggesting that these areas are receptive sites. These exposed areas appear as a string of beads [8].

A large proportion of articular sensory neurons are peptidergic. The major neuropeptides in joint nerves are substance P, calcitonin gene-related peptide and somatostatin. Neurokinin A, galanin, enkephalins and neuropeptide Y have also been localized in joint afferents. Neuropeptides influence the inflammatory process in the periphery and modify spinal processing of joint input [6]. They may also act on the primary afferent neurons themselves (see below).

Responses of Joint Afferents to Mechanical Stimulation of the Normal Joint

Response properties of articular afferents have been investigated in several species using electrophysiological recordings from single fibers. Since the TMJ is difficult to study with the necessary techniques, few data from the TMJ are directly available. Most data are from articular nerves supplying the cat knee, rat knee and ankle joint. In these experiments, fibers with conduction velocities in the Aβ, Aδ and C fiber range were characterized for their thresholds to local mechanical stimulation and for their responses to innocuous and noxious passive movements of the joint. Innocuous stimuli are light to moderate pressure applied to the joint (which evoke only nonpainful pressure perceptions) and movements within the working range of the joint that are normally not painful. Noxious stimuli are strong pressure at intensities that are felt as pain, and movements exceeding the working range of the joint, such as twisting against the resistance of the tissue. Different types of fibers have been found [9]. Figure 1 shows joint afferents recorded from the medial articular nerve of the cat knee joint.

Figure 1a displays a low-threshold Aδ fiber with two receptive fields in the fibrous capsule (dots) that responded phasically to extension of the knee. This fiber was strongly activated by inward rotation within the working range of the knee joint. The strongest responses were elicited by noxious movements, such as noxious inward rotation. Typically, these neurons are also activated by light pressure applied to the receptive field. This response pattern is observed for the majority of the fast-conducting Aβ fibers with corpuscular endings [10], for about one third of the Aδ fibers and for a small percentage of C fibers [6, 9].

The Aδ fiber in figure 1b with a receptive field in the patellar ligament (dot) shows a weak response (few action potentials) during outward rotation in the working range and a strong response to noxious outward rotation. This response pattern is observed most often in Aβ fibers, but also in Aδ and in a small proportion of C fibers [6, 9].

Figure 1c shows a specific nociceptive C fiber with a receptive field in the fibrous capsule. It did not respond to any innocuous movement but showed pronounced responses when the joint was twisted (noxious outward rotation). These neurons require also a high pressure intensity to elicit a response by probing the receptive field. Such a pattern was found for a small proportion of Aβ fibers and for about one third of Aδ and C fibers [6, 9].

Figure 1d displays an Aδ fiber with a receptive field in the anterior capsule that did not respond to any innocuous and noxious movement but did so to noxious pressure onto the receptive field. This response pattern was found in about 25% of the Aδ fibers and in more than one third of the C fibers [6, 9].

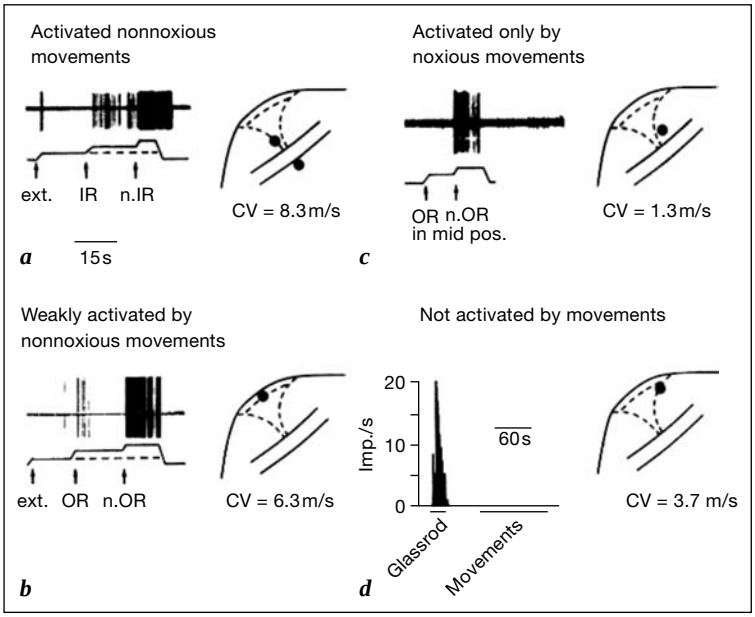

Fig. 1a–d. Four different articular afferents of the knee joint of a cat exemplifying classes of afferents according to their responses to passive movements. CV = Conduction velocity; Dots in the insets = receptive fields identified by probing the joint; ext. = extension; imp. = impulses; IR = inward rotaton (pronation); mid pos. = mid (resting) position; n.IR and n.OR = noxious IR and OR; OR = outward rotation (supination). From Schaible and Grubb [6].

Thus, many low-threshold Aβ and Aδ fibers in the fibrous capsule and in ligaments including the anterior cruciate ligament [11] fire in the innocuous range, but they have their strongest response in the noxious range. Responses to innocuous stimuli might be used to control movements and to prevent unphysiological movements. Most likely, these fibers cause the pressure sensations that can be elicited from the joint (see above). Although higher discharge rates encode the strength of a stimulus from the innocuous to the noxious range, they do not encode the presence of a noxious stimulus per se. In fact, the most adequate innocuous mechanical stimulus can evoke a stronger response than a noxious mechanical stimulus, e.g. a noxious movement into another direction. By contrast, noxious stimuli are adequately encoded by fibers that respond only very weakly or not to innocuous stimuli but show pronounced responses when noxious stimuli are applied.

Silent Fibers

All of the fibers described above had a receptive field in the joint, i.e. action potentials could be elicited by local mechanical stimulation of joint structures.

However, the joint nerve contains a further group of sensory neurons that are mechanoinsensitive (silent) under normal conditions. These neurons can be found when electrical stimulation of the joint nerve is used as searching stimulus. If an electrically identified fiber, in particular a C fiber, does neither respond to local mechanical stimulation of the knee nor to innocuous and noxious movements, several possibilities exist. First, the fiber may have a receptive field in a joint structure which cannot be accessed by local mechanical stimulation. Such a fiber could still respond to movements. Second, the fiber may be an efferent sympathetic one and thus does not respond to sensory stimulation. Third, the fiber may have such a high threshold that it does not respond to mechanical stimulation. As a further test, we used intra-arterial injection close to the joint of a solution containing a high concentration of KCl because afferent fibers with a receptive field usually respond to this KCl bolus with a short burst of action potentials. Indeed, a high proportion of the mechanoinsensitive fibers showed a response to KCl injection suggesting that these fibers are afferent without having a response to mechanical stimulation. Finally, we noted that many of these fibers are becoming mechanosensitive to local stimulation when the joint is inflamed (see next paragraph). Therefore, we concluded that at least a proportion of the silent fibers are initially mechanoinsensitive or silent nociceptors [12–14].

It is difficult to make a precise estimation of the proportion of silent nociceptors in the joint nerve. However, presumably about one third of the C fibers and some Aδ fibers are silent nociceptors. Because these units are not excited by noxious mechanical stimuli to the normal joint, they do not seem to contribute to pain perceptions elicited by twisting the joint; nonetheless, they are important during inflammation (see next paragraph).

Silent nociceptors have also been identified in cutaneous and visceral nerves. Silent nociceptors in the skin do not respond to noxious mechanical and thermal stimuli applied to normal skin, but some of them are chemosensitive and show a particular long-lasting response to algogenic chemical stimuli [15–17]. Thus, they play an important role in mediating neurogenic inflammation in humans [18]. There is evidence that silent nociceptors have distinct axonal biophysical characteristics separating them from polymodal nociceptors [17, 19]. In the viscera, silent nociceptors were described that lack mechanosensitivity under normal conditions, but become mechanosensitive during inflammation [20, 21].

Sensitization of Joint Afferents for Mechanical Stimuli during Inflammation

An inflamed joint hurts during movements in the working range and during palpation, and pain may occur under resting conditions. An important

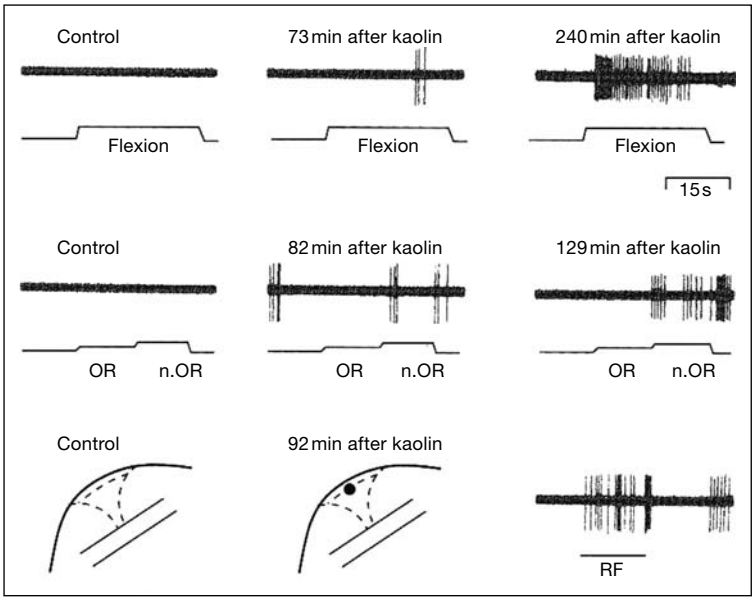

Fig. 2. Induction of mechanosensitivity in an initially mechanoinsensitive (silent) C fiber of a cat's knee joint. No responses to mechanical stimulation (probing, movements) before inflammation (control). Generation of responses to movements and pressure during development of inflammation after kaolin/carrageenan-induced knee inflammation. n.OR = Noxious outward rotation; OR = outward rotation; RF = receptive field. From Schaible and Schmidt [14].

mechanism for the heightened pain sensitivity is the increase in mechanosensitivity in joint afferents. Several distinct changes are induced when the joint is becoming inflamed. First, some low-threshold Aβ fibers show transiently increased responses to joint movements in the initial hours of inflammation. They do not develop resting discharges. Second, low-threshold Aδ and C fibers show increased responses to movements in the working range. Third, a large proportion of high-threshold Aδ and C fibers (see fig. 1c, d) are sensitized so that they respond to movements in the working range of the joint. Many units develop ongoing discharges in the resting position. Fourth, initially mechanoinsensitive afferents (silent nociceptors) are sensitized and become mechanosensitive [12–14, 22, 23]. Thus, the peripheral neuronal basis of inflammatory pain is the sensitization of mechanosensitive afferents plus the recruitment of silent nociceptors. From studies in humans it was concluded that mechanoinsensitive nociceptors play a major role in initiating central sensitization [24] (below).

Figure 2 shows the induction of mechanosensitivity in an initially mechanoinsensitive C fiber by inflammation. This unit was identified by electrical

stimulation of the joint nerve but it did not respond to mechanical stimulation of the normal joint (control). It had neither a detectable receptive field in the joint nor was it activated by any innocuous and noxious movements of the joint. The fiber was then further monitored after induction of an acute inflammation in the knee by the intra-articular injection of kaolin and carrageenan. During development of inflammation the unit began to respond to movements of the inflamed joint, and a receptive field could be identified in the anterior region by probing the joint with a glass rod, obviously because it had been sensitized to mechanical stimulation in the course of inflammation.

Chemosensitivity of Joint Afferents

The key to mechanosensitivity changes of sensory Aδ and C fibers is their chemosensitivity. A large proportion of these fibers express receptors for endogenous compounds that are produced and released during pathophysiological conditions. Mediators are able to excite and/or sensitize primary afferent neurons for mechanical and chemical stimuli. Usually, these mediators produce also vascular and other changes in the tissue, i.e. they contribute to the inflammatory process itself.

Effects of mediators on joint afferents have recently been summarized [25] (see also the chapter by Kopp and Sommer, pp 28–43). The classical inflammatory mediators bradykinin, prostaglandins E_2 and I_2, and serotonin excite joint afferents and sensitize them for mechanical stimuli. Common properties of these mediators are: (i) that they only affect Aδ and C, not Aβ fibers; (ii) that an effect is only elicited in subpopulations of the units; (iii) that high-threshold as well as low-threshold Aδ and C fibers are affected or not affected, and (iv) that some initially mechanoinsensitive afferent fibers are sensitized and become mechanosensitive. Whether the mode of sensitization is principally different for mechanosensitive and mechanoinsensitive joint afferents has not been systematically explored.

Prostaglandin E_2 and bradykinin together can cause a stronger sensitization to mechanical stimulation than bradykinin or prostaglandin E_2 alone. Conversely, nonsteroidal anti-inflammatory drugs such as aspirin and indomethacin reduce spontaneous discharges from acutely and chronically inflamed joints and attenuate the responses to mechanical stimulation. Adenosine triphosphate, adenosine, capsaicin and ananadamide excite a proportion of joint afferents (the latter indicate the presence of the vanilloid receptor subtype 1). Substance P increased, while somatostatin reduced mechanosensitivity in numerous afferents; the peptides galanin, neuropeptide Y and nociceptin sensitized some neurons and reduced responses in other neurons.

Whether the different patterns of peptide effects (excitation or inhibition) are dependent on the functional state of the neuron is not known at the moment. In general, it was proposed that the simultaneous presence of different neuropeptides regulates the excitability of the afferent fibers. Recordings from afferent fibers from normal and inflamed joints revealed that the proportion of neurons that show an effect of a mediator can be different under normal and inflammatory conditions. Whether this shows regulation of receptor expression or changes in the milieu needs to be established [25].

Release of Mediators, in Particular of Neuropeptides, from Joint Afferents

A significant proportion of joint afferents are peptidergic (see above). Neuropeptides are released from the peripheral and spinal endings of the fibers. In particular the release of substance P, neurokinin A and calcitonin gene-related peptide has been studied. The *peripheral* release of neuropeptides produces neurogenic inflammation which is thought to aggravate inflammatory lesions. The *spinal* release of these neuropeptides is involved in the generation and maintenance of spinal hyperexcitability as a consequence of joint inflammation [25].

Primary afferents contribute to central sensitization by the intraspinal release of glutamate [26, 27] and neuropeptides [28–30]. When the knee is normal, noxious but not innocuous compression of the joint enhances the intraspinal release of substance P, neurokinin A and calcitonin gene-related peptide above baseline. These data suggest that these neuropeptides are mainly synthesized in and released from high-threshold afferents. However, during acute inflammation joint afferents are sensitized, and, therefore, they release neuropeptides even when the joint is stimulated at innocuous intensity [28–30] (see also the chapter by Kopp and Sommer, pp 28–43, for data on the inflamed TMJ). These peptides facilitate the responses of spinal cord neurons, and they may ‘open’ synaptic pathways so that more neurons respond to stimulation [25]. Whether silent nociceptors of the joint significantly contribute to the release of neuropeptides has not been systematically explored because it has been impossible to stimulate mechanoinsensitive afferent fibers selectively. However, data from silent nociceptors of the human skin suggest that these receptors play an important role in mediating neurogenic inflammation [18] and a major role in initiating central sensitization [24]. Although silent nociceptors in the TMJ have not been directly studied, it is very likely that processes analogous to those outlined above are relevant in the generation of TMJ pain.

References

1 Kellgren JH: Some painful joint conditions and their relation to osteoarthritis. Clin Sci 1939;4:193–205.
2 Kellgren JH, Samuel EP: The sensitivity and innervation of the articular capsule. J Bone Joint Surg 1950;4:193–205.
3 Lewis T: Suggestions relating to the study of somatic pain. Br Med J 1938;i:321–325.
4 Lewis T: Pain. London, McMillan, 1942.
5 Scott DL: Osteoarthritis and rheumatoid arthritis; in McMahon SB, Koltzenburg M (eds): Wall and Melzack's Textbook of Pain, ed 5. London, Elsevier, 2006, pp 653–667.
6 Schaible HG, Grubb BD: Afferent and spinal mechanisms of joint pain. Pain 1993;55:5–54.
7 Johannson H, Sjölander P, Sojka P: Receptors in the knee joint ligaments and their role in biomechanics of the joint. CRC Crit Rev Biomed Eng 1991;18:341–368.
8 Heppelmann B, Messlinger K, Neiss W, Schmidt RF: Ultrastructural three-dimensional reconstruction of group III and group IV sensory nerve endings (free nerve endings) in the knee joint capsule of the rat: evidence for multiple receptive sites. J Comp Neurol 1990;292:103–116.
9 Schaible HG, Schmidt RF: Responses of fine medial articular nerve afferents to passive movements of knee joint. J Neurophysiol 1983;49:1118–1126.
10 Dorn T, Schaible HG, Schmidt RF: Response properties of thick myelinated group II afferents in the medial articular nerve of normal and inflamed knee joints of the cat. Somatosens Mot Res 1991;8:127–136.
11 Krauspe R, Schmidt M, Schaible HG: Sensory innervation of the anterior cruciate ligament: an electrophysiological study of the response properties of single identified mechanoreceptors in the cat. J Joint Bone Surg 1992;7:390–397.
12 Grigg P, Schaible HG, Schmidt RF: Mechanical sensitivity of group III and IV afferents from posterior articular nerve in normal and inflamed cat knee. J Neurophysiol 1986;55:635–643.
13 Schaible HG, Schmidt RF: Effects of an experimental arthritis on the sensory properties of fine articular afferent units. J Neurophysiol 1985;54:1109–1122.
14 Schaible HG, Schmidt RF: Time course of mechanosensitivity changes in articular afferents during a developing experimental arthritis. J Neurophysiol 1988;60:2180–2195.
15 Ringkamp M, Peng YB, Wu G, Hartke TV, Campbell JN, Meyer RA: Capsaicin responses in heat-sensitive and heat-insensitive A-fiber nociceptors. J Neurosci 2001;21:4460–4468.
16 Schmelz M, Schmidt R, Handwerker HO, Torebjörk HE: Encoding of burning pain from capsaicin-treated human skin in two categories of unmyelinated nerve fibers. Brain 2000;123:560–571.
17 Weidner C, Schmelz M, Schmidt R, Hansson B, Handwerker HO, Torebjörk HE: Functional attributes discriminating mechano-insensitive and mechano-responsive C nociceptors in human skin. J Neurosci 1999;19:10184–10190.
18 Schmelz M, Michael K, Weidner C, Schmidt R, Torebjörk HE, Handwerker HO: Which nerve fibers mediate the axon reflex flare in human skin? Neuroreport 2000;11:645–648.
19 Orstavik K, Weidner C, Schmidt R, Schmelz M, Hilliges M, Jørum E, Handwerker HO, Torebjörk HE: Pathological C-fibers in patients with a chronic painful condition. Brain 2003;126:567–578.
20 Cervero F, Laird JM: Visceral pain. Lancet 1999;353:2145–2148.
21 Häbler HJ, Jänig W, Koltzenburg M: A novel type of unmyelinated chemosensitive nociceptor in the acutely inflamed urinary bladder. Agents Actions 1988;25:219–221.
22 Coggeshall RE, Hong KAP, Langford LA, Schaible HG, Schmidt RF: Discharge characteristics of fine medial articular afferents at rest and during passive movements of inflamed knee joints. Brain Res 1983;272:185–188.
23 Guilbaud G, Iggo A, Tégner R: Sensory receptors in ankle joint capsules of normal and arthritic rats. Exp Brain Res 1985;58:29–40.
24 Klede M, Handwerker HO, Schmelz M: Central origin of secondary mechanical hyperalgesia. J Neurophysiol 2003;90:353–359.
25 Schaible HG: Basic mechanisms of deep somatic pain; in McMahon SB, Koltzenburg M (eds): Wall and Melzack's Textbook of Pain, ed 5. London, Elsevier, 2006, pp 621–633.

26 Sluka KA, Westlund K: An experimental arthritis in rats: dorsal horn aspartate and glutamate increases. Neurosci Lett 1992;145:141–144.
27 Yang LC, Marsala M, Yaksh TL: Characterization of time course of spinal amino acids, citrulline and PGE_2 release after carrageenan/kaolin-induced knee inflammation: a chronic microdialysis study. Pain 1996;67:345–354.
28 Hope PJ, Jarrott B, Schaible HG, Clarke RW, Duggan AW: Release and spread of immunoreactive neurokinin A in the cat spinal cord in a model of acute arthritis. Brain Res 1990;533:292–299.
29 Schaible HG, Jarrott B, Hope PJ, Duggan AW: Release of immunoreactive substance P in the cat spinal cord during development of acute arthritis in cat's knee: a study with antibody bearing microprobes. Brain Res 1990;529:214–223.
30 Schaible HG, Freudenberger U, Neugebauer V, Stiller U: Intraspinal release of immunoreactive calcitonin gene-related peptide during development of inflammation in the joint in vivo – A study with antibody microprobes in cat and rat. Neuroscience 1994;62:1293–1305.

Prof. Dr. med. Hans-Georg Schaible
Institut für Physiologie I, Lehrstuhl für Neurophysiologie
Universität Jena, Teichgraben 8
DE–07743 Jena (Germany)
Tel. +49 36 41 93 88 10, Fax +49 36 41 93 88 12, E-Mail hans-georg.schaible@mti.uni-jena.de

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 28–43

Inflammatory Mediators in Temporomandibular Joint Pain

Sigvard Kopp[a], *Claudia Sommer*[b]

[a]Department of Clinical Oral Physiology, Institute of Odontology, Karolinska Institutet, Huddinge, Sweden; [b]Neurologische Klinik der Universität Würzburg, Würzburg, Germany

Abstract

Inflammation in the synovial tissues plays a major role in determining whether a temporomandibular joint (TMJ) problem becomes painful. Prostaglandins, serotonin and pro-inflammatory cytokines are the major inflammatory mediators in the TMJ. Here we describe the technique of arthrocentesis, which is necessary to obtain a reproducible determination of inflammation in the TMJ. Levels of inflammatory mediators were found to be increased in the synovial fluid (SF) of patients with TMJ pain compared to controls and correlated positively with local pain. Intra-articular injections of glucocorticosteroids reduce subjective symptoms and clinical signs of TMJ disease, partially by inhibited neuropeptide and cytokine release, but also by local and systemic serotonergic mechanisms. A high pretreatment level of tumor necrosis factor α (TNF-α) in the TMJ SF is a predictor for a positive response to glucocorticosteroids. Furthermore, systemic treatment with a combination of the TNF-α blocker infliximab and methotrexate reduces TMJ pain in patients with rheumatoid arthritis through an increase in anti-inflammatory cytokines and receptors, indicating an important role of the cytokine system in this subgroup. In conclusion, the presence of inflammatory mediators in the SF of the TMJ is a strong indication of a local inflammatory disorder and may predict the treatment effect.

A large body of evidence has accumulated showing that inflammation in the synovial tissues plays a major role in determining whether a temporomandibular joint (TMJ) problem becomes painful and which is the prognosis upon treatment. Pain may be a consequence of malocclusion, disk displacement and other mechanical dysfunctions, but the underlying mechanisms for the development of pain are almost always of inflammatory nature. Much has been learned from the pathophysiology of rheumatoid arthritis, where the role of

activated T cells, macrophages and plasma cells in the synovial tissue, with expression of a large number of inflammatory mediators, has long been known and has recently become a target for treatment [1]. The inflammatory mediators most thoroughly investigated and thought to be most prevalent are the prostaglandins, mainly prostaglandin E_2 (PGE_2), serotonin (5-HT) and the proinflammatory cytokines and their antagonists.

Temporomandibular disorders, including pain of muscular origin, are related to generalized painful disorders like the fibromyalgia syndrome, where these mediators are also reported to play a role [2]. Recent data show that not only the absolute levels of the inflammatory mediators, but also the balance between the pro- and anti-inflammatory substances may determine the degree of pain in a certain disorder and the propensity for chronification [3]. Furthermore, neuroendocrine mechanisms have been explored, revealing that inflammatory responses are modulated by a bidirectional communication between the neuroendocrine and the immune system [4]. Neuroendocrine peptides are released in the synovial tissues from primary afferent nerves (e.g. substance P, calcitonin gene-related peptide) or sympathetic efferents (neuropeptide Y) and contribute to the inflammatory process and pain in the TMJ.

This chapter summarizes the present knowledge on the role of inflammatory mediators in TMJ pain with a background of pathophysiological mechanisms and discusses consequences drawn from these findings for the treatment of TMJ pain.

Recent Advances on How Inflammatory Mediators Elicit Pain

Prostaglandins

Prostaglandins act as hormones in a number of systemic physiological and local pathophysiological processes, including pain, edema, fever and inflammation. Prostaglandins, mainly PGE_2 and PGI_2, are rapidly produced following tissue injury or inflammation by most cells at the site of injury in response to noxious stimuli mainly by the inducible form of cyclooxygenase 2. In muscle, cytokines, in particular tumor necrosis factor (TNF) α, can induce their upregulation [5]. They are stored in phospholipids on the cell membrane and cleaved by phospholipase A_2 on receptor-mediated or receptor-independent stimulation. Peripherally administered prostaglandins produce hyperalgesia in humans and experimental animals. Injections of PGE_2 and PGI_2 are thought to produce hyperalgesia by acting directly on the peripheral terminals of primary afferent nociceptors [6]. The increase in neuronal activity results from lowering the activation threshold for opening of tetrodotoxin-resistant sodium channels like Na_v 1.8 by phosphorylation of these channels via phosphokinase A [7].

Serotonin

5-HT has recently come back into the focus of research as a peripheral algesic mediator. In peripheral tissues, 5-HT is considered proalgesic [8], but 5-HT acting on $5\text{-HT}_{1B/D}$ receptors in the trigeminal system blocks the release of neuropeptides. Thus, these diverse interactions of 5-HT and its numerous receptors complicate our understanding of its role in painful conditions like TMJ pain. The 5-HT content in peripheral tissues increases rapidly in inflammation or injury, the main cellular sources of 5-HT in peripheral tissues being platelets and mast cells. There is indirect evidence that 5-HT may have a stronger effect on lesioned or inflamed tissues than on intact ones [9, 10]. However, recently, 5-HT and a 5-HT_3 receptor agonist were shown to sensitize C fibers in isolated segments of rat sural nerve, independent of whether or not a previous lesion existed [8]. In most preparations, 5-HT is more potent in enhancing algesic effects of other mediators than in inducing pain by itself [11, 12]. 5-HT can sensitize nerve fibers to the actions of bradykinin, indicating an effect on bradykinin receptors. On the other hand, the 5-HT_3 receptor, itself a ligand-gated ion channel, may directly enhance neuronal activity. 5-HT modulates tetrodotoxin-resistant sodium currents, where it increases the magnitude of the current, shifts its conductance-voltage relationship to a hyperpolarized direction and increases its rate of activation and inactivation [7]. In healthy volunteers, 5-HT infused into muscle did not induce pain or hyperalgesia by itself, but sensitized the tissue to bradykinin [13]. Injections of a higher concentration of 5-HT into the masseter muscle in healthy human females induced pain and hyperalgesia [14], which could be reversed by the 5-HT_3 antagonist granisetron [15]. Interestingly, pain or hyperalgesia did not increase after injection of 5-HT into the masseter muscle of patients with fibromyalgia [14].

Cytokines

Like prostaglandins, cytokines are produced locally and mainly exert their effects over short distances onto nearby cells. Therefore, in most pathological states, systemic measurements of cytokine levels do not adequately reflect local pathology. As in the example of TMJ disease, local cytokine levels are higher and probably of more diagnostic value than circulating blood levels (fig. 1).

Synthesis of cytokines is initiated by signaling through toll-like receptors that recognize host-derived molecules released from injured tissues [17]. Whether directly or indirectly, the proinflammatory cytokines activate genes for inflammatory molecules, such as cyclooxygenase 2, nitric oxide synthases and phospholipases. Cytokines have direct and indirect algesic and hyperalgesic effects. For example interleukin (IL) 1β induces production of nitric oxide, bradykinin and prostaglandins. Furthermore, it has a direct excitatory action on nociceptive fibers, which are activated within 1 min by IL-1β application [18]. Brief exposure of the skin to IL-1β facilitates heat-evoked calcitonin gene-related

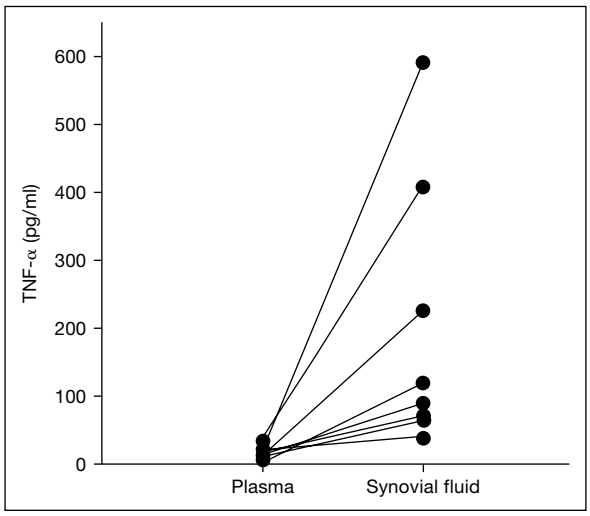

Fig. 1. Plasma (mean = 17 pg/ml, SD = 6) and TMJ synovial fluid (mean = 201 pg/ml, SD = 198) TNF-α concentrations for 8 patients with chronic TMJ arthritis and detectable levels of TNF-α in the synovial fluid. There was a significant difference between plasma and synovial fluid concentrations ($p = 0.001$). Published with permission from Elsevier Publishing Company, originally published in the *Journal of Oral and Maxillofacial Surgery* [16], p 528.

peptide release [19]. In vitro perfusion of TNF-α to dorsal root ganglia elicits neuronal discharges in both A and C fibers [20]. Downstream of TNF-α receptor activation, hyperalgesia induced by nerve injury is mediated via p38 mitogen-activated protein kinase [21]. This kinase, in turn, phosphorylates tetrodotoxin-resistant sodium channels, which leads to an increased excitability of nociceptors [22]. The TNF-α inhibitor etanercept reduces both allodynia and p38 mitogen-activated protein kinase phosphorylation, indicating that the TNF-α-p38 signal transduction cascade in the dorsal root ganglia is a significant participant in the generation of mechanical allodynia.

It appears that the balance of pro- and anti-inflammatory cytokines is at least as important as absolute levels of individual cytokines. In our own series of 45 patients with chronic widespread pain, we found decreased levels of anti-inflammatory cytokines compared to controls [3]. A deficiency in the anti-inflammatory mediators IL-1 receptor antagonist, IL-10 and TGF-β was also found in patients with TMJ pain [23, 24]. IL-4 and the related cytokine IL-13 reduce pain in various models [25–27]. IL-10 pretreatment reduces the hyperalgesic responses to intraplantar injections of carrageenin, IL-1β, IL-6 and TNF-α [28] and to nerve injury [29].

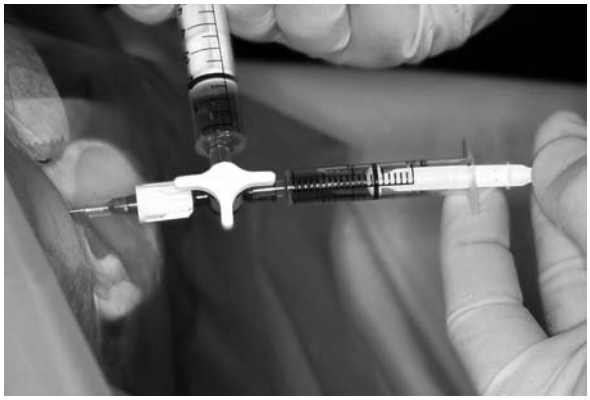

Fig. 2. SF sampling of the TMJ by the push-and-pull technique. The 4-ml sampling solution, which consists of physiological saline (78%) and Behepan (22%), is injected with the larger syringe and aspirated with the smaller. The shift in red color of vitamin B_{12} is used for spectrophotometric measurement in the quantification procedure of SF. Published with permission from S. Karger AG, Basel, originally published in *Cells Tissues Organs* [31], p 24.

Measurement of Inflammatory Mediator Levels in the TMJ Synovial Fluid

Technique for Synovial Fluid Sampling and Analysis

The synovial fluid (SF) sampling technique (arthrocentesis) suggested below has been described before [30] and has been used and validated in numerous studies (fig. 2). The sampling procedure requires some skill, and investigators have to be trained thoroughly before the technique can be adopted for clinical use or scientific investigations. Before arthrocentesis, the joint should be carefully palpated during mandibular movements to locate the condyle and the mandibular fossa. The fossa is felt as a depression anterior to the tragus upon mouth opening. Hair over the joint is shaved, and any hair in the vicinity of the joint is held aside. A head cap can be used to cover the remaining hair. The skin area 4–5 cm around the injection site is cleansed with benzalkonium chloride (0.1%), iodine (5%) and alcohol (70%). A surgical drape (e.g. Steri-Drape TM, No. 1020) with a 6-cm hole in the center is placed over the joint to maintain a clean area. The operator should wear gloves and a face mask. A mouth prop makes maintaining the mouth opening during the injection less cumbersome for the patient.

Anesthesia of the TMJ is preferred and achieved by an auriculotemporal nerve block with e.g. 2.0 ml Xylocain (lidocaine 2%, Astra, Södertälje, Sweden) with a fine needle (0.4 × 20 mm). The TMJ is then punctured with a standard needle (23 G, 0.6 × 25–40 mm) inserted into the posterior part of the upper joint compartment. With the patient's mouth open, the needle is inserted into the fossa

2–3 mm beneath the zygomatic arch and 8–10 mm anterior to the anterior border of the tragus. These landmarks may vary, so palpation of the condyle and fossa is important. The needle is directed perpendicularly for the first 10–15 mm and then slightly upward and backward to account for the angulation of the condyle. If resistance is felt, it may have penetrated the posterior part of the disk and not the upper joint space proper. This may occur in patients with restricted condylar translation. The needle should not be forced further, but withdrawn and the insertion tried again. Scratching of the articular surfaces by the needle should be avoided. When properly positioned, the needle should have penetrated 20–30 mm beneath the skin surface depending on the thickness of the subcutaneous fat layer. TMJ SF samples are obtained by washing the joint cavity with saline using a push and pull technique performed with two syringes (4 ml; fig. 2), one used for the washing solution to be injected and the other for aspiration, connected to the arthrocentesis needle by a 3-way stopcock. The injection solution, which consists of 78% saline (NaCl 9 mg/ml; Kabi Pharmacia, Uppsala, Sweden) and 22% Behepan® (1 mg/ml, hydroxocobalamin, vitamin B_{12}; Kabi Pharmacia), is injected slowly into the joint cavity, 1 ml at a time, and then aspirated. The correct intra-articular position of the arthrocentesis needle can be confirmed by easy flow of the washing solution when injected and aspirated. The total washing solution volume used is 4 ml. The syringe may then be detached, and another syringe containing a drug can be attached and a therapeutic injection made. The needle is then removed, and slight pressure is maintained over the injection site for 1–2 min with a gauze dressing. A dressing may be placed over the injection site, but bleeding is a very uncommon occurrence. Antibiotics are unnecessary because infection following an intra-articular injection is extremely rare.

The hydroxocobalamin is included in order to measure the dilution of the washing solution in the aspirate, i.e. for an indirect measurement of the SF content in the aspirate. The washing solutions before injection and after aspiration are compared in a spectrophotometer (Shimadzo UV-160A; Shimadzo Corp., Tokyo, Japan) with a capillary tube system consisting of a capillary tube of quartz (0.7 mm in diameter for a 3-μl sample) and a capillary tube holder (Shimadzo Corp.). The detection limit for the dilution of the washing solution after aspiration by this method is 0.9%. The SF concentration of any particular substance (SF–) can then be calculated using the formula:

$$C_S = \frac{C_A}{\left(1 - \frac{Abs_{Asp}}{Abs_{Wash}}\right)}$$

where C_S = SF concentration, C_A = aspirate concentration, Abs_{Asp} = aspirate absorbance and Abs_{Wash} = washing solution absorbance.

Table 1. Findings on inflammatory mediators in the SF of the TMJ in healthy individuals and patients with TMJ disease

	Healthy controls	Patients	Reference No.
SP	n.d.	present	[32]
CGRP	n.d.	present	[32]
NPY	n.d.	present	[33]
PGE_2	negative	present	[34]
5-HT	negative	present	[35]
TNF-α	negative	present	[16, 31]
TNFsRII	negative	high	[31]
IL-1β	negative or low	present	[14, 36, 37]
IL-6	negative	high	[38]
IL-1sRII	n.d.	high	[24, 39, 40]
IL-1ra	n.d.	high	[23, 31, 39]
IL-10	negative	negative	[23]
TGF-β	negative	present	[23]

CGRP = Calcitonin gene-related peptide; IL-1ra = IL-1 receptor antagonist; IL-1sRII = soluble receptor II of IL-1; n.d. = not determined; NPY = neuropeptide Y; SP = substance P; TGF-β = transforming growth factor β; TNFsRII = soluble receptor II of TNF.

During and immediately after the arthrocentesis, blood cell contamination of the aspirate is checked visually. Blood cell contamination, especially by erythrocytes, can be observed in this solution, almost as easily as in pure saline. Blood contamination of the aspirate will interfere with the calculation of SF concentrations. After aspiration, the weight of the sample is immediately measured and the sample is centrifuged (1,500 g for 10 min in 4°C) and hemolysis is then recorded as absent or present by visual inspection. Twelve microliters of the supernatant, i.e. 4 capillary tubes, are used for the absorbance measurement. The aspirated and preinjection washing solution absorbances are compared, and a dilution factor (DF = Abs_{Asp}/Abs_{Wash}) is calculated for each. The remaining part of the supernatant is transferred to tubes, one for each substance to be analyzed, and stored in a freezer (–85°C) until analysis. The recommended sample quality criteria are based on sample hemolysis (should be absent), blood contamination (should be absent or hardly visible), aspirate volume (>0.5 ml) and dilution factor/recovery of SF (<0.98).

Inflammatory Mediators in the TMJ in Healthy Individuals and Patients

Data collected in our laboratory (S.K.) and a brief survey of the literature are summarized in table 1. Briefly, in the SF of the TMJ, 5-HT levels were

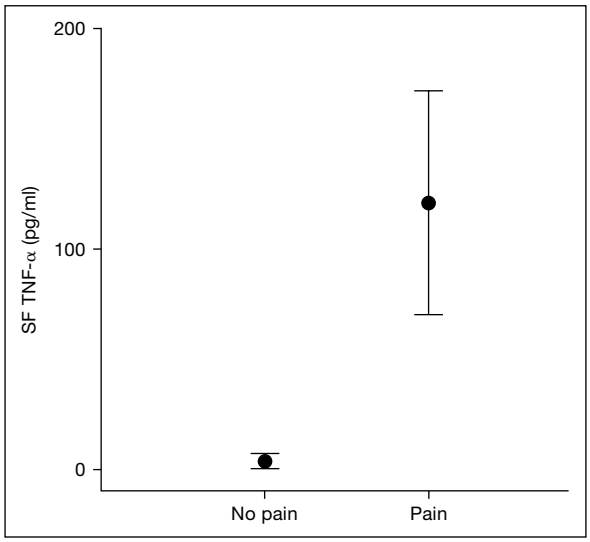

Fig. 3. SF concentrations of TNF-α in patients with chronic TMJ arthritis and pain (mean = 120 pg/ml, SEM = 51, n = 13) and without pain at maximum mandibular opening (mean = 3 pg/ml, SEM = 3, n = 11). There was a significant difference between the groups (p = 0.010). Published with permission from Elsevier Publishing Company, originally published in the *Journal of Oral and Maxillofacial Surgery* [16], p 528.

correlated with pain upon movement [41]. PGE_2 was also increased in patients compared to controls, and the levels were correlated with pain upon movement [34]. TNF-α levels were significantly higher in patients with TMJ pain than in those without such pain [16] (fig. 3). A correlation was also found between TNF-α levels and tenderness to palpation of the posterior aspect of the TMJ, which indicates that it contributes to local hyperalgesia [16]. High TNF levels have also been implicated to predict poor outcome of surgical interventions [42]. IL-1β levels also correlated with TMJ pain [36]. The presence of the IL-1 receptor antagonist was associated with lower intensity pain [39]. Other investigators found IL-6 more often in patients with TMJ pain compared to controls and found a correlation of IL-6 levels and pain [38].

Influence of Local and Systemic Treatment on Inflammatory Mediators and Pain in the TMJ

Local Treatment with Glucocorticoids

The anti-inflammatory effect of intra-articularly administered glucocorticoids in joints with painful arthritis is well documented. Intra-articular

corticosteroids are useful in alleviating pain, swelling and impaired function following inflammatory diseases involving the TMJ, such as rheumatoid arthritis (RA), as well as in primarily noninflammatory joint diseases such as osteoarthrosis [42]. Glucocorticoids act on cytoplasmic glucocorticoid receptors that inhibit the expression of genes for proinflammatory cytokines such as TNF-α and increase the expression of genes encoding anti-inflammatory cytokines such as the soluble receptor II of TNF-α, which has been shown to reduce arthritis [44]. Glucocorticoids have an inhibitory effect on inflammatory mediator release from many cell types involved in inflammation such as macrophages, T lymphocytes, mast cells, dendritic cells and neutrophilic leukocytes. The synthesis of PGE is reduced by inhibiting the production of arachidonic acid from cellular phospholipids by inhibition of the phospholipase A_2 enzyme [43]. Glucocorticoids also stabilize the membrane of the lysosomes of damaged cells and thereby prevent the release of proteolytic enzymes and inhibit enzymes already released. They further inhibit the synthesis of proteoglycans and collagen, which is a side effect and may impair the healing process. This factor is important with long-term systemic administration, but not with limited numbers of intra-articular injections. Local side effects of intra-articular injection of glucocorticoids, such as destruction of articular cartilage, have been reported [45]. The cause of these deleterious effects has not been fully explained, and adequate controls are lacking. On the contrary clinical studies have shown that intra-articular glucocorticoid injections result in less release of proteoglycan into the joint fluid than before treatment and recurrence of symptoms coincided with an increase in proteoglycan in the SF [46]. A recent study showed that repeated intra-articular glucocorticoid administration every third month for 2 years in the knee joint with osteoarthrosis was not associated with radiological progress compared with a control group [47].

Intra-articular injections of glucocorticosteroids into the TMJ have been advocated in patients with acute synovitis secondary to osteoarthrosis and in patients with acute exacerbations of inflammatory joint disease, e.g. RA. This recommendation is supported by substantial evidence and is associated with minimal side effects [43]. Besides RA and osteoarthrosis, intra-articular glucocorticoid injections are effective in inflamed joints with psoriatic arthropathy, ankylosing spondylitis, gout, chondrocalcinosis, reactive arthritis and rheumatic fever.

A long-term study of treatment with intra-articular glucocorticoids showed a significant effect on nonsystemic arthritis of the TMJ with subjective symptoms and clinical signs such as joint tenderness, maximum voluntary mouth opening and bite force, while neither joint crepitation nor muscle tenderness was affected by the treatment [48]. In a randomized, double-blind clinical trial of intra-articular methylprednisolone acetate (Depo-Medrol) in patients with

RA of the TMJ, this glucocorticoid had a significant short-term effect on both pain and tenderness that exceeded the effect of saline [49].

In a study of the TMJ, intra-articular administration of glucocorticoid caused a short-term decrease in the level of neuropeptide Y in the SF from patients with inflammatory joint disease (RA), at the same time as pain and hyperalgesia of the joint were reduced [50]. These findings indicate that part of the pain-relieving effect of glucocorticoids is due to inhibited neuropeptide release from sympathetic nerve terminals involved in neurogenic inflammation.

A recent study showed that local and systemic serotonergic mechanisms modulate the effect of intra-articular glucocorticoid treatment on TMJ pain in patients with chronic TMJ arthritis of systemic nature, while changes in pressure pain threshold over the TMJ are mostly influenced by systemic serotonergic mechanisms [35]. Patients with detectable pretreatment levels of SF 5-HT experienced a larger decrease in TMJ pain intensity at rest than those without and, likewise, more relief from TMJ pain on movement. The pretreatment plasma level of 5-HT on the other hand was associated with less reduction of resting pain of the TMJ after treatment. There was no correlation between 5-HT in SF and plasma; however, the plasma level was correlated to C-reactive protein and thus to systemic inflammatory activity.

As can be expected, TNF-α levels in SF and plasma appear to be predictive for the treatment response to intra-articular administration of glucocorticoid into the TMJ. A high pretreatment level of TNF-α in the TMJ SF was found to be a positive predictor for relief of TMJ pain provoked by mandibular movement after intra-articular administration of glucocorticoid [51]. The pain relief was associated with TNF-α reduction after treatment. It is thus quite likely that TNF-α is involved in the modulation of this TMJ pain entity. There was no correlation between SF and plasma levels of TNF-α, and the SF level was higher than the plasma level which indicates a local production of the mediator in the TMJ synovial tissues (fig. 1).

*Systemic Treatment with the TNF-**α** Blocker Infliximab*

According to the data mentioned above, TNF-α can be suspected to be one important contributor to pain of the arthritic TMJ. Blocking of the production of TNF-α systemically or locally may thus be a rational therapy to alleviate TMJ inflammation and pain, like in patients with RA [52]. Systemic treatment with a combination of infliximab and methotrexate has been shown to reduce TMJ pain in RA with an increase in anti-inflammatory cytokines in SF and blood plasma [31]. TMJ pain intensity at rest and in movement as well as tenderness to digital palpation of the TMJ (hyperalgesia/allodynia) were reduced in parallel with global joint pain but not TMJ pressure pain thresholds. Both erythrocyte sedimentation rate and C-reactive protein decreased, which indicates that

the systemic inflammatory activity was also reduced. Both local and global decrease in pain was most probably a result of decreased local and systemic inflammation due to elimination of biologically active TNF-α [53]. However, the reduction of TMJ pain was associated with raised SF levels of soluble receptor II of TNF-α (fig. 4a) and soluble receptor II of IL-1 (fig. 4b) as well as raised plasma levels of IL-1 receptor antagonist and IL-10. This increase in anti-inflammatory cytokine and soluble receptor levels associated with the pain reduction indicates that endogenous cytokine control mechanisms also influence the response to infliximab treatment, e.g. by inhibition of the activation and sensitization of afferent nerves to the nociceptive effects of proinflammatory cytokines such as TNF-α and IL-1β. The effect of systemic treatment with a combination of infliximab and methotrexate therefore seems to depend on an increase in anti-inflammatory cytokines and receptors in SF and blood plasma.

The lack of treatment response for the pressure pain threshold of the TMJ is remarkable. There are reasons to believe that the pressure pain threshold, which can be categorized as allodynia or hyperalgesia, is an entity separate from joint pain at rest and in movement [41]. The lateral border of the TMJ is located about 15 mm beneath the skin surface and hyperalgesia detected by external pressure on the skin surface, corresponding to the low-pressure pain threshold, might be a secondary phenomenon or unrelated to TMJ pathology. The mechanisms behind a possible treatment response of the pressure pain threshold are therefore probably different from those of TMJ pain at rest or in movement.

In about a third of patients, there are no or only minor effects on TMJ pain intensity after systemic administration of infliximab and methotrexate [40]. The effect of infliximab on TMJ pain could be predicted by pretreatment plasma levels of IL-1β, IL-1 receptor antagonist and IL-10 as well as pretreatment levels of TMJ SF soluble receptor II of IL-1. High pretreatment levels of these cytokines and receptors as well as presence of rheumatoid factor were associated with no or minor reduction of TMJ pain after treatment. This negative effect of IL-1β must be independent of TNF-α since infliximab specifically inhibits TNF-α [54]. There are a number of TNF-α-independent pathways that may activate IL-1β production from monocytes. These pathways include neuropeptides, hormones, physical contact between T cells and macrophages as well as denatured matrix proteins [55]. In addition, the plasma level of IL-1β was not changed during treatment follow-up, which supports a negative TNF-α-independent influence of IL-1β on the treatment effect on TMJ pain.

The presence of rheumatoid factor is a negative factor influencing the treatment response of TMJ pain and this effect is independent from IL-1β. Seropositive patients have higher plasma levels of other mediators like

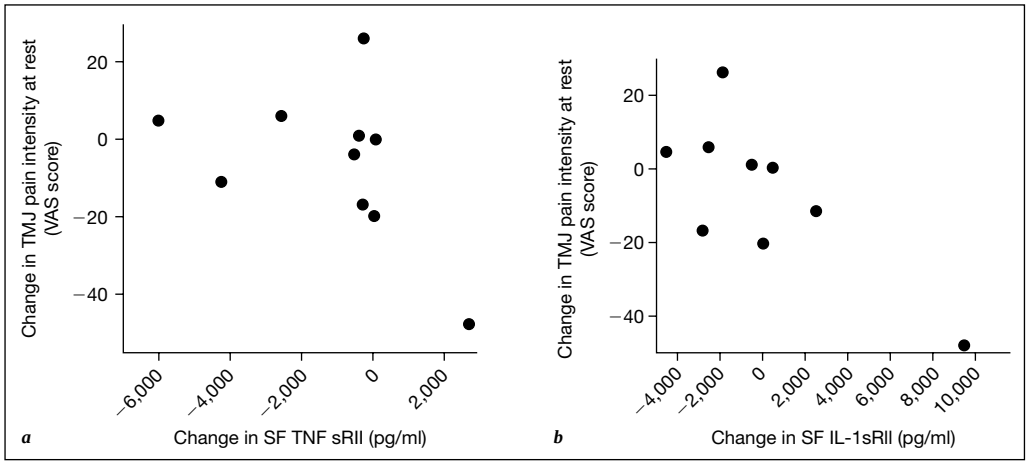

Fig. 4. The relation between change in TMJ resting pain intensity (millimeters on a 100-mm visual analogue scale, VAS) and change in TMJ SF levels of soluble receptor II of TNF (TNFsRII; $r_s = -0.73$, $p = 0.016$, $n = 10$; ***a***) and soluble receptor II of IL-1 (IL-1sRII; $r_s = -0.76$, $p = 0.016$, $n = 9$; ***b***) in patients with RA after treatment with infliximab and methotrexate at the short-term (2 weeks) follow-up. Published with permission from S. Karger AG, Basel, originally published in *Cells Tissues Organs* [31], p. 25.

serotonin, which levels in turn are related to inflammatory joint disease activity and pain. Activation of platelets and subsequent release of inflammatory mediators from these can be induced by the rheumatoid factor. In addition, the treatment response is poor when the anti-inflammatory cytokines are already highly expressed in synovial tissues and plasma before treatment. It is remarkable that systemic disease activity according to blood levels of C-reactive protein and IL-6 before treatment was not associated with the treatment response of TMJ pain. None of these in turn correlated with the pretreatment plasma level of IL-1β. For comparison, the pretreatment level of IL-1β in the SF of the knee was a negative predictor for reduction of the number of tender and swollen joints after systemic treatment with a combination of infliximab and methotrexate [S.K., unpubl. data]. A low pretreatment level of soluble receptor II of IL-1 in the SF was associated with reduction in global pain intensity, while a low pretreatment level of IL-10 was associated with reduction of the Disease Activity Score calculated on 28 joints including the number of tender and swollen joints, erythrocyte sedimentation rate and the patient's assessment of general health.

Local Treatment with Infliximab

A few case reports have been published about the intra-articular administration of infliximab into the knee joint with persistent inflammation due to RA. Intra-articular administration of infliximab seems to be effective and safe in patients with persistent monoarthritis due to RA [56] and ankylosing spondylitis [57] but there are divergent opinions about the long-term outcome of the treatment and whether the effect is superior to intra-articular corticosteroids [58]. In our clinic we have positive experience with treatment of the TMJ in a single patient, who is on a regimen of repeated infliximab injections and also receives systemic administration [S.K., unpubl. data].

Conclusions

The presence of inflammatory mediator levels in the SF fluid of the TMJ exceeding those in plasma is a strong indication of a local inflammatory disorder (arthritis) which is usually associated with pain.

Inflammatory mediators are important targets for local as well as systemic treatment.

Pretreatment levels of inflammatory mediators particularly in the SF but also in the blood may predict the treatment effect on inflammatory pain conditions of the TMJ.

References

1 Firestein GS: Immunologic mechanisms in the pathogenesis of rheumatoid arthritis. J Clin Rheumatol 2005;11:S39–S44.

2 Hedenberg-Magnusson B, Ernberg M, Alstergren P, Kopp S: Pain mediation by prostaglandin E_2 and leukotriene B_4 in the human masseter muscle. Acta Odontol Scand 2001;59:348–355.

3 Üceyler N, Valenza R, Stock M, Schedel R, Sprotte G, Sommer C: Lowered anti-inflammatory cytokine levels in patients with chronic widespread pain. Arthritis Rheum 2006;54:2656–2664.

4 Kopp S: Neuroendocrine, immune, and local responses related to temporomandibular disorders. J Orofac Pain 2001;15:9–28.

5 Schäfers M, Sorkin LS, Sommer C: Intramuscular injection of tumor necrosis factor-alpha induces muscle hyperalgesia in rats. Pain 2003;104:579–588.

6 Taiwo YO, Bjerknes LK, Goetzl EJ, Levine JD: Mediation of primary afferent peripheral hyperalgesia by the cAMP second messenger system. Neuroscience 1989;32:577–580.

7 Gold MS, Reichling DB, Shuster MJ, Levine JD: Hyperalgesic agents increase a tetrodotoxin-resistant Na^+ current in nociceptors. Proc Natl Acad Sci USA 1996;93:1108–1112.

8 Moalem G, Grafe P, Tracey DJ: Chemical mediators enhance the excitability of unmyelinated sensory axons in normal and injured peripheral nerve of the rat. Neuroscience 2005;134:1399–1411.

9 Aley KO, Messing RO, Mochly-Rosen D, Levine JD: Chronic hypersensitivity for inflammatory nociceptor sensitization mediated by the epsilon isozyme of protein kinase C. J Neurosci 2000;20:4680–4685.

10 Song XJ, Zhang JM, Hu SJ, LaMotte RH: Somata of nerve-injured sensory neurons exhibit enhanced responses to inflammatory mediators. Pain 2003;104:701–709.

11 Lang E, Novak A, Reeh PW, Handwerker HO: Chemosensitivity of fine afferents from rat skin in vitro. J Neurophysiol 1990;63:887–901.
12 Abbott FV, Hong Y, Blier P: Activation of 5-HT_{2A} receptors potentiates pain produced by inflammatory mediators. Neuropharmacology 1996;35:99–110.
13 Babenko V, Svensson P, Graven-Nielsen T, Drewes AM, Jensen TS, Arendt-Nielsen L: Duration and distribution of experimental muscle hyperalgesia in humans following combined infusions of serotonin and bradykinin. Brain Res 2000;853:275–281.
14 Ernberg M, Lundeberg T, Kopp S: Pain and allodynia/hyperalgesia induced by intramuscular injection of serotonin in patients with fibromyalgia and healthy individuals. Pain 2000;85:31–39.
15 Ernberg M, Lundeberg T, Kopp S: Effect of propranolol and granisetron on experimentally induced pain and allodynia/hyperalgesia by intramuscular injection of serotonin into the human masseter muscle. Pain 2000;84:339–346.
16 Nordahl S, Alstergren P, Kopp S: Tumor necrosis factor α in synovial fluid and plasma from patients with chronic connective tissue disease and its relation to temporomandibular joint pain. J Oral Maxillofac Surg 2000;58:525–530.
17 Kariko K, Weissman D, Welsh FA: Inhibition of toll-like receptor and cytokine signaling – A unifying theme in ischemic tolerance. J Cereb Blood Flow Metab 2004;24:1288–1304.
18 Fukuoka H, Kawatani M, Hisamitsu T, Takeshige C: Cutaneous hyperalgesia induced by peripheral injection of interleukin-1β in the rat. Brain Res 1994;657:133–140.
19 Opree A, Kress M: Involvement of the proinflammatory cytokines tumor necrosis factor α, IL-1β and IL-6 but not IL-8 in the development of heat hyperalgesia: effects on heat-evoked calcitonin gene-related peptide release from rat skin. J Neurosci 2000;20:6289–6293.
20 Schäfers M, Lee DH, Brors D, Yaksh TL, Sorkin LS: Increased sensitivity of injured and adjacent uninjured rat primary sensory neurons to exogenous tumor necrosis factor α after spinal nerve ligation. J Neurosci 2003;23:3028–3038.
21 Schäfers M, Svensson CI, Sommer C, Sorkin LS: Tumor necrosis factor α induces mechanical allodynia after spinal nerve ligation by activation of p38 MAPK in primary sensory neurons. J Neurosci 2003;23:2517–2521.
22 Jin X, Gereau RW: Acute p38-mediated modulation of tetrodotoxin-resistant sodium channels in mouse sensory neurons by tumor necrosis factor α. J Neurosci 2006;26:246–255.
23 Fang PK, Ma XC, Ma DL, Fu KY: Determination of interleukin-1 receptor antagonist, interleukin-10, and transforming growth factor β_1 in synovial fluid aspirates of patients with temporomandibular disorders. J Oral Maxillofac Surg 1999;57:922–928, discussion 928–929.
24 Tominaga K, Habu M, Sukedai M, Hirota Y, Takahashi T, Fukuda J: IL-1β, IL-1 receptor antagonist and soluble type II IL-1 receptor in synovial fluid of patients with temporomandibular disorders. Arch Oral Biol 2004;49:493–499.
25 Cunha FQ, Poole S, Lorenzetti BB, Veiga FH, Ferreira SH: Cytokine-mediated inflammatory hyperalgesia limited by interleukin 4. Br J Pharmacol 1999;126:45–50.
26 Lorenzetti BB, Poole S, Veiga FH, Cunha FQ, Ferreira SH: Cytokine-mediated inflammatory hyperalgesia limited by interleukin 13. Eur Cytokine Netw 2001;12:260–267.
27 Hao S, Mata M, Glorioso JC, Fink DJ: HSV-mediated expression of interleukin 4 in dorsal root ganglion neurons reduces neuropathic pain. Mol Pain 2006;2:6.
28 Poole S, Cunha FQ, Selkirk S, Lorenzetti BB, Ferreira SH: Cytokine-mediated inflammatory hyperalgesia limited by interleukin 10. Br J Pharmacol 1995;115:684–688.
29 Wagner R, Janjigian M, Myers RR: Anti-inflammatory interleukin 10 therapy in CCI neuropathy decreases thermal hyperalgesia, macrophage recruitment, and endoneurial TNF-α expression. Pain 1998;74:35–42.
30 Alstergren P, Ernberg M, Kopp S, Lundeberg T, Theodorsson E: TMJ pain in relation to circulating neuropeptide Y, serotonin, and interleukin 1β in rheumatoid arthritis. J Orofac Pain 1999;13:49–55.
31 Kopp S, Alstergren P, Ernestam S, Nordahl S, Morin P, Bratt J: Reduction of temporomandibular joint pain after treatment with a combination of methotrexate and infliximab is associated with changes in synovial fluid and plasma cytokines in rheumatoid arthritis. Cells Tissues Organs 2005;180:22–30.
32 Alstergren P, Appelgren A, Appelgren B, Kopp S, Lundeberg T, Theodorsson E: Co-variation of neuropeptide Y, calcitonin gene-related peptide, substance P and neurokinin A in joint fluid from patients with temporomandibular joint arthritis. Arch Oral Biol 1995;40:127–135.

33 Appelgren A, Appelgren B, Kopp S, Lundeberg T, Theodorsson E: Relation between the intra-articular temperature of the temporomandibular joint and the presence of neuropeptide Y-like immunoreactivity in the joint fluid: a clinical study. Acta Odontol Scand 1993;51:1–8.
34 Alstergren P, Kopp S: Prostaglandin E_2 in temporomandibular joint synovial fluid and its relation to pain and inflammatory disorders. J Oral Maxillofac Surg 2000;58:180–186, discussion 186–188.
35 Fredriksson L, Alstergren P, Kopp S: Serotonergic mechanisms influence the response to glucocorticoid treatment in TMJ arthritis. Mediators Inflamm 2005;2005:194–201.
36 Alstergren P, Ernberg M, Kvarnstrom M, Kopp S: Interleukin 1β in synovial fluid from the arthritic temporomandibular joint and its relation to pain, mobility, and anterior open bite. J Oral Maxillofac Surg 1998;56:1059–1065, discussion 1066.
37 Nordahl S, Alstergren P, Eliasson S, Kopp S: Interleukin 1β in plasma and synovial fluid in relation to radiographic changes in arthritic temporomandibular joints. Eur J Oral Sci 1998;106: 559–563.
38 Shinoda C, Takaku S: Interleukin 1β, interleukin 6, and tissue inhibitor of metalloproteinase 1 in the synovial fluid of the temporomandibular joint with respect to cartilage destruction. Oral Dis 2000;6:383–390.
39 Alstergren P, Benavente C, Kopp S: Interleukin 1β, interleukin 1 receptor antagonist, and interleukin 1 soluble receptor II in temporomandibular joint synovial fluid from patients with chronic polyarthritides. J Oral Maxillofac Surg 2003;61:1171–1178.
40 Kopp S, Alstergren P, Ernestam S, Nordahl S, Bratt J: Interleukin-1β influenced the effect of infliximab on temporomandibular joint pain in rheumatoid arthritis. Scand J Rheumatol 2006;35: 182–188.
41 Alstergren P, Kopp S: Pain and synovial fluid concentration of serotonin in arthritic temporomandibular joints. Pain 1997;72:137–143.
42 Shafer DM, Assael L, White LB, Rossomando EF: Tumor necrosis factor α as a biochemical marker of pain and outcome in temporomandibular joints with internal derangements. J Oral Maxillofac Surg 1994;52:786–791.
43 Barnes PJ: Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci (Lond) 1998;94:557–572.
44 Cuzzocrea S, Ayroldi E, Di Paola R, Agostini M, Mazzon E, Bruscoli S, Genovese T, Ronchetti S, Caputi AP, Riccardi C: Role of glucocorticoid-induced TNF receptor family gene (GITR) in collagen-induced arthritis. Faseb J 2005;19:1253–1265.
45 Lundberg IE, Grundtman C, Larsson E, Klareskog L: Corticosteroids – From an idea to clinical use. Best Pract Res Clin Rheumatol 2004;18:7–19.
46 Saxne T, Heinegard D, Wollheim FA: Therapeutic effects on cartilage metabolism in arthritis as measured by release of proteoglycan structures into the synovial fluid. Ann Rheum Dis 1986;45: 491–497.
47 Raynauld JP, Buckland-Wright C, Ward R, Choquette D, Haraoui B, Martel-Pelletier J, Uthman I, Khy V, Tremblay JL, Bertrand C, Pelletier JP: Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2003;48:370–377.
48 Kopp S, Carlsson GE, Haraldson T, Wenneberg B: Long-term effect of intra-articular injections of sodium hyaluronate and corticosteroid on temporomandibular joint arthritis. J Oral Maxillofac Surg 1987;45:929–935.
49 Kopp S, Akerman S, Nilner M: Short-term effects of intra-articular sodium hyaluronate, glucocorticoid, and saline injections on rheumatoid arthritis of the temporomandibular joint. J Craniomandib Disord 1991;5:231–238.
50 Alstergren P, Appelgren A, Appelgren B, Kopp S, Lundeberg T, Theodorsson E: The effect on joint fluid concentration of neuropeptide Y by intra-articular injection of glucocorticoid in temporomandibular joint arthritis. Acta Odontol Scand 1996;54:1–7.
51 Fredriksson L, Alstergren P, Kopp S: Tumor necrosis factor alpha in temporomandibular joint synovial fluid predicts treatment effects on pain by intra-articular glucocorticoid treatment. Cells Tissues Organs, in press.

52 Choy EH, Smith C, Dore CJ, Scott DL: A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal. Rheumatology (Oxford) 2005;44:1414–1421.
53 Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, Breedveld FC, Smolen JS, Eberl G, de Woody K, Feldmann M, Maini RN: Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-α therapy in rheumatoid arthritis. J Immunol 1999;163: 1521–1528.
54 van den Berg WB: Anti-cytokine therapy in chronic destructive arthritis. Arthritis Res 2001;3: 18–26.
55 Isler P, Vey E, Zhang JH, Dayer JM: Cell surface glycoproteins expressed on activated human T cells induce production of interleukin 1β by monocytic cells: a possible role of CD69. Eur Cytokine Netw 1993;4:15–23.
56 Nikas SN, Temekonidis TI, Zikou AK, Argyropoulou MI, Efremidis S, Drosos AA: Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study. Ann Rheum Dis 2004;63:102–103.
57 Schatteman L, Gyselbrecht L, De Clercq L, Mielants H: Treatment of refractory inflammatory monoarthritis in ankylosing spondylitis by intraarticular injection of infliximab. J Rheumatol 2006;33:82–85.
58 Bokarewa M, Tarkowski A: Local infusion of infliximab for the treatment of acute joint inflammation. Ann Rheum Dis 2003;62:783–784.

Sigvard Kopp, DDS, PhD, Odont dr
Professor
Department of Clinical Oral Physiology
Institute of Odontology, Karolinska Institutet
Alfred Nobels Allé 8, Box 4064
SE–141 04 Huddinge (Sweden)
Tel. +46 8 728 82 81, Fax +46 8 608 08 81, E-Mail sigvard.kopp@ofa.ki.se

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 44–55

The Role of Reproductive Hormones in Orofacial Pain

Linda LeResche

Department of Oral Medicine, University of Washington, Seattle, Wash., USA

Abstract

It has long been recognized that more women than men present for treatment of certain orofacial pain conditions. Evidence is accumulating that at least some of this discrepancy is due to the influence of female reproductive hormones on orofacial pain. The use of hormone replacement therapy in women is associated with a moderately increased risk of developing temporomandibular pain. However, temporomandibular pain is perceived to be of the highest intensity at times of low or fluctuating endogenous estrogen. Most research concerning hormonal effects on burning mouth and atypical odontalgia/persistent idiopathic facial pain has examined the effect of exogenous hormones. Although there are certainly indications that hormonal factors play a role in these pain conditions, more research is needed to clarify these associations. A range of peripheral and central pain mechanisms have been investigated in an attempt to explain the observed gender patterns in clinical pain conditions and the assumed relationship between hormonal factors and orofacial pain. At this point, some studies indicate that the presence of female reproductive hormones enhances pain response, while other studies suggest that these hormones decrease pain response. These seemingly contradictory findings could be explained if hormones act differently in peripheral tissues and at different levels of the nervous system.

It has long been recognized that more women than men present for treatment of certain orofacial pain conditions, such as temporomandibular muscle and joint disorders (TMJDs) and burning mouth syndrome (BMS). Epidemiological evidence suggests that many orofacial pain problems are more common among women than among men in the community as well [1–3]. Gender differences have been found both in the prevalence of orofacial pain problems (i.e. the percentage of the population experiencing the pain condition during a particular time period) and in incidence rates (i.e. rates of onset over a specific time period). There are a number of possible reasons for these gender

Table 1. Population-based prevalence studies of pain in the temporomandibular region

Authors	Prevalence, %		Female:male ratio	Peak age years
	women	men		
Helkimo [8]	14.0	10.0	1.4	35–44
Szentpétery et al. [9]	8.3	3.2	2.6	not reported
Locker and Slade [7]	9.5	5.0	1.9	<45
Von Korff et al. [5]	15.0	8.0	1.9	25–44
Salonen et al. [10]	12.0	8.0	1.5	none
Goulet et al. [6]	9.0	5.0	1.8	35–54

discrepancies, including cultural and psychosocial factors [4]. However, evidence is accumulating that at least some of the discrepancy is due to the influence of female reproductive hormones on orofacial pain. This chapter will review the clinical and epidemiological evidence concerning the relationship of reproductive hormones to specific orofacial pain conditions in women. Information concerning the possible mechanisms of action of reproductive hormones on chronic orofacial pain conditions will also be presented.

Age and Gender Differences in the Prevalence of Orofacial Pain Conditions

Musculoskeletal Pain Conditions

The most common chronic orofacial pain conditions involve pain in the temporomandibular joint (TMJ) and associated masticatory muscles. In North America, pain in the temporomandibular region affects approximately 10% of the adult population [2, 5–7]. Prevalence rates in women are about 1.5–2 times those of men, and prevalence peaks around the age of 40 and declines thereafter (table 1). Prior to puberty, prevalence rates of temporomandibular pain are relatively similar for males and females [11], although the rates and gender prevalence ratios differ across studies to a greater extent than for adults. A recent investigation of 12- to 19-year-olds conducted in Sweden [12] found prevalence rates to differ only slightly in boys and girls before the age of 15. However, by the age of 16, the adult pattern of a prevalence ratio of 2:1 or more in favor of women was established. In another study, girls were found to be significantly more likely to experience a first onset of temporomandibular pain between the

ages of 11 and 14 years than were boys [13], and, for girls, the probability of experiencing temporomandibular pain increased with time since menarche [14]. This pattern of increasing gender discrepancy around the time of puberty and declining prevalence around the usual time of menopause suggests that reproductive hormones may play a role in temporomandibular pain conditions.

Neuropathic Pain Conditions and Chronic Pain of Unknown Origin

Age and gender differences in incidence are also apparent for trigeminal neuralgia (TN) [15]. In addition, BMS, atypical odontalgia and persistent idiopathic (formerly 'atypical') facial pain all seem to be more common in women than in men [16–18], at least among treated cases. These latter conditions, once considered to be of unknown origin, are now thought by many investigators [19, 20] to be neuropathic in nature, or at least to have neuropathic components.

Classically defined TN is a rare condition, with only 3–5 onsets per year per 100,000 people [3]. Epidemiological data on TN are very limited. Some large studies indicate a gender difference in incidence, with onset rates in women about 1.5–1.7 times those in men [15, 21], although another large study found a female:male ratio of only 1:1.1 [22]. All studies agree that TN increases with age, and it appears that the gender difference is found in all age groups between the ages of 35 and 75 years [15]. A recent study of TN diagnosed in primary care [23], which used a broader case definition, found a similar pattern of rising incidence with age and higher rates in women at all ages, although overall incidence rates in this study were much higher than those found in studies using a narrower case definition. Nevertheless, none of these studies found dramatic changes in rates of onset of TN around the time of puberty or menopause, suggesting that, if reproductive hormones play a role in the gender differences in onset observed for TN, these factors act indirectly through their influence on early development.

A small number of population-based studies have assessed the prevalence of BMS [2, 24–26]. These studies have found rates of BMS ranging between 0.6 and almost 15%, depending on the case definition and the population studied. The prevalence of BMS is consistently found to increase with age. Although some of the population-based studies, including the largest [2], have found a female predominance in BMS prevalence, one investigation found no significant gender differences in prevalence rates in a population 65 years of age or older [24]. It may be, however, that BMS symptoms are severer in women than in men, or that more cases of BMS are not attributable to specific causes (e.g. candidiasis) in women. Clinical studies almost universally report that the majority of patients with idiopathic BMS are peri- or postmenopausal women [18], and gender ratios in the order of 4–5 women for every man are typical in clinic populations [27].

There are virtually no population-based studies of persistent idiopathic facial pain. However, in a systematic review [27] of 8 clinical studies or case series ranging in size from 32 to 121 patients with persistent idiopathic facial pain, the mean age of subjects was 40–60 years, and the proportion of female subjects ranged from 62 to 89%. In the two largest samples (121 and 95 subjects), the proportions of female subjects were 83 and 86%, respectively.

Population-based research on the prevalence pattern of atypical ondontalgia (i.e. intraoral neuropathic pain) is also lacking. However, the majority of cases are generally found to be in their 40s [16, 17]. One recent review of clinical studies [16] summarized female:male prevalence ratios in the clinical studies reviewed as ranging from 2:1 to 20:1. In another review [17], which included data on sample size, female:male gender ratios were 2:1 and 4:1 in the two clinical studies with sample sizes of 50 patients or more.

In summary, both musculoskeletal orofacial pain and other orofacial pain conditions that may have neuropathic features are more prevalent in women than in men. There are a number of possible reasons for these prevalence discrepancies, including anatomical and psychosocial differences between the sexes. However, prevalence patterns showing changes in prevalence in females at hormonal transition points (puberty, menopause) may indicate that reproductive hormones play a role in the pain condition. Thus, it appears plausible that reproductive hormones may be involved in temporomandibular pain, BMS, atypical odontalgia and persistent idiopathic facial pain. The evidence for such involvement is reviewed in the next section.

Hormones and Musculoskeletal Orofacial Pain

Exogenous Hormones

Although the evidence is somewhat contradictory [28–33], a number of studies suggest that the use of exogenous hormones – oral contraceptives and hormone replacement therapy (HRT) – may be associated with an increased risk of temporomandibular pain. Two early studies compared the oral contraceptive histories of treated female TMJD cases to those of age-matched controls. One investigation [28] found cases to report a significantly higher use of oral contraceptives, while the other [29] found a lower rate of use among the cases. Larger, population-based studies have either found no significant relationship between oral contraceptive use and orofacial pain (including, but not limited to temporomandibular pain) [30] or found only a slightly increased risk of TMJDs among the oral contraceptive users [31]. Thus, if there is an association between the use of oral contraceptives and musculoskeletal orofacial pain, it is likely that the relationship is not strong. However, examination of the use of oral

contraceptives may not provide the most powerful test of the hypothesis that reproductive hormones are involved in temporomandibular pain, since both users and nonusers of oral contraceptives can be expected to have circulating levels of some form of estrogen and progesterone within the biologically active range.

On the other hand, levels of circulating hormones are likely to be substantially different in postmenopausal women who use HRT and those who do not. In a large case-control study of postmenopausal women (1,291 women with TMJDs and 5,164 age-matched controls) selected from the databases of a prepaid health plan, women using HRT were found to be at higher risk of being referred for care of pain associated with TMJDs than women not using HRT [31]. Specifically, the risk of TMJD pain was related to estrogen use, with a clear dose-response relationship between the amount of estrogen prescribed in the prior year and the risk of TMJDs. Among women at the highest cumulative estrogen dose, the risk of TMJD pain was roughly double that for women not using estrogen. A population-based study of 510 postmenopausal women found no relationship between the use of estrogen HRT in the prior 2 weeks and the severity of TMJD signs and symptoms, including pain [32]. However, due to differences in the designs, case definitions and sample sizes of the two studies, as well as the fact that the increased risk in the case-control study was only of moderate size, the failure of the second study to replicate the first is, perhaps, not surprising [33]. On the other hand, another population-based study, which included 435 postmenopausal women, again found a moderate relationship between HRT use and orofacial pain, including, but not limited to musculoskeletal pain symptoms (age-adjusted odds ratio = 1.46, 95% confidence interval = 1.02–2.08) [30].

Thus, the evidence, while not definitive, suggests a modest relationship between the use of HRT and temporomandibular pain. In such naturalistic studies, it is possible that an association between HRT and temporomandibular pain is attributable to some other factor or factors that may influence both pain and HRT use. The most obvious of these factors would be the general tendency to experience and seek treatment for symptoms. However, all three of the studies cited above used multivariate models that controlled for this factor in one way or another. Thus, it appears that, if HRT use influences the risk of temporomandibular pain, the effect is not solely attributable to a general tendency to experience and use health care for somatic symptoms.

Endogenous Hormones

A number of studies have examined whether the risk of temporomandibular pain and/or levels of temporomandibular pain vary with naturally occurring changes in reproductive hormones. Dao et al. [34] conducted a pilot study of pain variability across the menstrual cycle among 12 women with myofascial

temporomandibular pain. Five of the women were using oral contraceptives and 7 were not. Pain levels were similar in the two groups. Although no patterns were apparent across the menstrual cycle, oral contraceptive use appeared to decrease the variability in pain levels.

Our own research [35] indicates that in women meeting research diagnostic criteria [36] for both myofascial pain and temporomandibular joint arthralgia, levels of pain in the temporomandibular region vary systematically across the menstrual cycle, showing a pattern of highest pain at times in the cycle when estrogen is typically at its lowest level, or when the estrogen level is rapidly changing. Our research also suggests that temporomandibular pain varies over the course of pregnancy, with lower pain levels during the 2nd and 3rd trimesters, when estrogen levels are high [37]. In the pregnancy study, pain levels showed a significant negative correlation with salivary levels of both estradiol and progesterone. (Both hormones vary in a similar fashion over pregnancy.)

The finding that exogenous estrogen use is associated with a moderately increased risk of developing temporomandibular pain and the finding that the highest temporomandibular pain levels in women occur at times of low or fluctuating endogenous estrogen may appear contradictory. However, the typical levels of estrogen in HRT are quite low – about the same as the lowest levels that occur during the normal menstrual cycle. If estrogen serves as a pain modulator in humans, as appears to be the case in animals [38], it may be that *low* levels of estrogen are associated with increased pain. Taken together, however, the existing evidence appears to indicate that hormonal factors play a role in musculoskeletal orofacial pain. The evidence is strongest for estrogen. Nonetheless, possible effects of progesterone cannot be ruled out at this point.

Hormones in Other Orofacial Pain Conditions

Because of the fact that the majority of clinical cases of unexplained BMS occur in postmenopausal women, several studies have investigated the effectiveness of HRT as a treatment for BMS [18, 39–42]. It appears that, at least for some women, HRT (most probably estrogen) has a positive effect on the thickness or maturation of the oral epithelium [39, 40]. Some studies [40, 41] also found an improvement in symptoms, but the sample sizes in these studies were small, follow-up periods were short, and neither subjects nor investigators were blinded. To our knowledge, only one double-blind placebo-controlled trial has examined the effect of HRT on oral symptoms [42]. Oophorectomized women (n = 145) were randomly assigned to receiving daily doses of mestranol (a form of estrogen) or placebo, and symptoms were compared at 1 year.

There were no significant differences in the prevalence of burning mouth symptoms in the two groups. On the other hand, some epidemiological studies have found HRT to *increase* the risk of burning mouth symptoms [43–45]. Two of these studies [43, 44] were population-based surveys (involving 1,017 and 3,173 women, respectively) that identified HRT as a significant risk factor for burning mouth symptoms, even after controlling for other relevant risk factors.

There has been little work on the potential association of HRT and atypical odontalgia or persistent idiopathic facial pain. One study [46] compared 44 clinical cases of persistent idiopathic facial pain (including atypical odontalgia) with 88 control women of similar age seeking care in a primary care clinic. Multivariate logistic regression analysis controlling for age, education, occupation and other relevant risk factors showed that HRT use was a significant independent predictor of persistent idiopathic facial pain (odds ratio = 4.6, 95% confidence interval = 1.5–13.8). Interestingly, the risk of persistent idiopathic facial pain was also significantly increased among women with endometriosis (odds ratio = 6.8, 95% confidence interval = 1.3–34.8).

Most of the research concerning possible hormonal effects on burning mouth and atypical odontalgia/persistent idiopathic facial pain has examined the effect of exogenous hormones. To our knowledge, there are no studies examining whether variability in these symptoms is associated with variability in levels of endogenous hormones. Although there are certainly indications of associations between hormonal factors and these pain conditions, obviously more research is needed to clarify these associations.

Mechanisms of Hormonal Involvement in Orofacial Pain

There are sex differences in the size of orofacial structures that are likely ultimately attributable to hormonal differences. These anatomical differences and associated biomechanical differences may influence the predisposition to injury or the rate of healing of these structures and could explain some of the observed sex differences in rates of orofacial pain disorders. However, in addition to these indirect hormonal effects, there appear to be direct effects of reproductive hormones on orofacial pain mechanisms. A range of peripheral and central pain mechanisms have been investigated in an attempt to explain the observed gender patterns in clinical pain conditions and the assumed relationship between hormonal factors and orofacial pain. This section provides a selective overview of the basic research evidence concerning effects of reproductive hormones on pain mechanisms. Most of this research has focused specifically on the effects of estrogen.

Hormonal Influences in Peripheral Tissues

Estrogen receptors have been found in the TMJ in a number of species [47], and estrogen has been shown to modulate inflammatory processes in the joint, although the specific mechanisms by which this modulation occurs are not totally clear. For example, in a complete Freund's adjuvant rat model, estradiol reduced the number of TMJ cells positively labeled for the inflammatory mediators tumor necrosis factor α, CD16 and double labeled CD14+/CD16+ in a dose-dependent manner. However, higher levels of estrogen were also associated with increased swelling in the TMJ [48].

Hormonal Influences on Responses to Painful Orofacial Stimuli

Reflex jaw muscle responses to injection of glutamate into the TMJ are of significantly greater magnitude in female than in male rats [49], and injection of glutamate into the masseter muscle in humans results in pain of higher peak intensity, longer duration and greater perceived spread in women than in men [50]. In rats, the response appears to be mediated by estrogen, as ovariectomy significantly decreased the magnitude of muscle response in females, while replacement of estrogen resulted in muscle activity levels similar to those of intact females.

In another study, nociceptive responses to a formalin injection into the TMJ were found to be lower in pregnant rats (i.e. with high estrogen levels) than in nonpregnant rats (i.e. with lower estrogen levels) [51]. Preinjection of the TMJ with a selective κ-opioid receptor agonist enhanced the behavioral nociceptive responses to formalin, suggesting that the antinociceptive effects of estrogen may be mediated by κ-opioids delivered in the periphery.

Hormonal Influences in the Trigeminal Ganglion

In the absence of painful stimuli, estrogen receptors as well as a number of neuropeptides in the trigeminal ganglion have been found to fluctuate with levels of ovarian steroids over the estrous cycle in mice [52]. In another investigation [53], hormonal fluctuations over the estrous cycle appeared to influence the ability of morphine to inhibit bradykinin-induced activity in TMJ-responsive neurons at the trigeminal nucleus caudalis/upper cervical cord junction. Opiate-based inhibitory mechanisms seemed to operate in males and in females with the low estrogen levels of diestrus, but not in females with the higher estrogen levels of proestrus.

Hormonal Influences on Higher Central Nervous System Pathways

In addition to specific hormonal effects in the trigeminal system, female reproductive hormones may affect pain neurotransmission and pain modulation pathways higher in the central nervous system. A series of elegant experiments

in mice has shown that different pathways predominate in mediating pain inhibition in males and females (summarized in Sternberg and Wachtermann [38]). Stress-induced (nonopioid) analgesia is mediated by N-methyl-D-aspartate (NMDA) in males. Although females show the same level of stress-induced analgesia as males and have the same NMDA-mediated anesthesia circuitry, hormonally intact females rely on hormonally-mediated pain inhibitory mechanisms, rather than NMDA systems. However, when females lack ovarian hormones, the NMDA system becomes active. Thus, there are qualitative differences in the pain modulation systems of males and females, at least in mice.

A recent human brain imaging study assessed endogenous opioid system responses to sustained facial pain induced by infusion of hypertonic saline into the masseter [54]. In healthy, normally cycling women, under conditions of low estradiol and progesterone (i.e., early follicular phase of the menstrual cycle), μ-opioid receptor-mediated neurotransmission, which modulates pain, was lower in women than in men in the anterior-medial thalamus, nucleus accumbens, ventral pallidum and amygdala (areas associated with pain) and was actually *de*activated in women [54, 55]. When exogenous estradiol was administered to the female subjects for 7–9 days during the follicular phase when estradiol levels would otherwise be low, the number of μ-opioid receptors in these regions increased to levels comparable to those of males and similar increases were observed in the response of the endogenous opioid system to sustained pain stimuli [54]. These studies suggest that while higher levels of estradiol can modulate pain in humans through activation of the μ-opioid system, low levels of estradiol may actually be associated with μ-opioid system deactivation and increased pain.

Summary of Hormonal Effects on Pain Mechanisms

At this point in the development of research, the results of some studies appear to indicate that the presence of female reproductive hormones enhances pain response, while other studies suggest that these hormones decrease pain response. In addition to obvious differences in experimental models, some of these seemingly contradictory findings may be explained if hormones act differently in peripheral tissues and at different levels of the nervous system.

Future Research Directions

Determination of the role of reproductive hormones in orofacial pain requires additional research at a number of levels. For musculoskeletal orofacial pain conditions, both clinical and basic research appear necessary to replicate initial findings and further explore potential mechanisms. For BMS, and especially for those conditions now called persistent idiopathic facial pain

and atypical odontalgia, clear, operational diagnostic criteria are required in order for epidemiological research to determine whether the age and gender distributions seen in clinical settings reflect the distribution of the conditions in the community. Animal models of these conditions should also be developed or existing models exploited to explore sex differences and hormonal influences.

Although most of the existing research on the role of reproductive hormones in orofacial pain has focused on estrogen, it is possible that other hormones, including not only progesterone, but also relaxin and testosterone, may be involved in some orofacial pain conditions. In the last 15 years, we have learned a great deal about the role of hormonal factors in orofacial pain, but investigations to date have addressed only a fraction of the relevant research questions. The next few years should provide research findings that will help fill the gaps in existing knowledge and lead to an increased understanding of the role of reproductive hormones in orofacial pain.

References

1 LeResche L: Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Crit Rev Oral Biol Med 1997;8:291–305.
2 Lipton JA, Ship JA, Larach-Robinson D: Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 1993;124:115–121.
3 LeResche L: Epidemiology of orofacial pain; in Lund JP, Lavigne G, Dubner R, Sessle B (eds): Orofacial Pain: From Basic Science to Clinical Management. Carol Stream, Quintessence, 2000, pp 15–25.
4 LeResche L: Sex, gender and clinical pain; in Flor H, Kalso E, Dostrovsky JO (eds): Proceedings of the 11th World Congress on Pain. Seattle, IASP Press, 2006, pp 543–554.
5 Von Korff M, Dworkin SF, LeResche L, Kruger A: An epidemiologic comparison of pain complaints. Pain 1988;32:173–183.
6 Goulet JP, Lavigne GJ, Lund JP: Jaw pain prevalence among French-speaking Canadians in Quebec and related symptoms of temporomandibular disorders. J Dent Res 1995;74:1738–1744.
7 Locker D, Slade G: Prevalence of symptoms associated with temporomandibular disorders in a Canadian population. Community Dent Oral Epidemiol 1988;16:310–313.
8 Helkimo M: Studies on function and dysfunction of the masticatory system. IV. Age and sex distribution of symptoms of dysfunction of the masticatory system in Lapps in the north of Finland. Acta Odont Scand 1974;32:255–267.
9 Szentpétery A, Huhn E, Fazekas A: Prevalence of mandibular dysfunction in an urban population in Hungary. Community Dent Oral Epidemiol 1986;14:177–180.
10 Salonen L, Hellden L, Carlsson GE: Prevalence of signs and symptoms of dysfunction in the masticatory system: an epidemiological study in an adult Swedish population. J Craniomandib Disord Facial Oral Pain 1990;4:241–250.
11 Drangsholt M, LeResche L: Temporomandibular disorder pain; in Crombie IK, Croft PR, Linton SJ, LeResche L, Von Korff M (eds): Epidemiology of Pain. Seattle, IASP Press, 1999, pp 203–233.
12 Nilsson IM, List T, Drangsholt M: Prevalence of temporomandibular pain and subsequent dental treatment in Swedish adolescents. J Orofac Pain 2005;19:144–150.
13 LeResche L, Mancl LA, Drangsholt MT, Huang G, Von Korff M: Predictors of onset of facial pain and temporomandibular disorders in early adolescence. Pain 2007; in press.

14 LeResche L, Mancl LA, Drangsholt M, Von Korff MR: Dating the onset of gender differences in TMD pain prevalence (abstract 2728). J Dent Res 2005, 84(special issue A). www.dentalresearch.org.
15 Katusic S, Beard CM, Bergstralh E, Kurland L: Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. Ann Neurol 1990;27:89–95.
16 Woda A, Pionchon P: A unified concept of idiopathic orofacial pain: clinical features. J Orofac Pain 1999;13:172–184.
17 Melis M, Lobo SL, Ceneviz C, Zawawi K, Al-Badawi E, Maloney G, Mehta N: Atypical odontalgia: a review of the literature. Headache 2003;43:1060–1074.
18 Ship JA, Grushka M, Lipton JA, Mott AE, Sessle BJ, Dionne RA: Burning mouth syndrome: an update. J Am Dent Assoc 1995;126:842–853.
19 Jaaskelainan SK: Clinical neurophysiology and quantitative sensory testing in the investigation of orofacial pain and sensory function. J Orofac Pain 2004;18:85–107.
20 Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, Padovani A, Sapelli P: Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 2005;115:332–337.
21 Manzoni GC, Torelli P: Epidemiology of typical and atypical craniofacial neuralgias. Neurol Sci 2005;26(suppl 2):s65–s67.
22 Rothman KJ, Monson RR: Epidemiology of trigeminal neuralgia. J Chron Dis 1973;26:3–12.
23 Hall GC, Carroll D, Parry D, McQuay HJ: Epidemiology and treatment of neuropathic pain: the UK primary care perspective. Pain 2006;122:156–162.
24 Riley JL 3rd, Gilbert GH, Heft MW: Orofacial pain symptom prevalence: selective sex differences in the elderly? Pain 1998;76:97–104.
25 Tammiala-Salonen T, Hiidenkari T, Parvinen T: Burning mouth in a Finnish adult population. Community Dent Oral Epidemiol 1993;21:67–71.
26 Locker D, Grushka M: The impact of dental and facial pain. J Dent Res 1987;66:1414–1417.
27 Zakrzewska JM, Hamlyn PJ: Facial pain; in Crombie IK, Croft PR, Linton SJ, LeResche L, Von Korff M (eds): Epidemiology of Pain. Seattle, IASP Press, 1999, pp 171–202.
28 Abubaker AO, John F, Sotereanos GC, Patterson G, Jenosky J: Prevalence of female sex hormone use by female TMJ patients. J Dent Res 1992;71(special issue):259.
29 Marbach JJ, Lennon MC, Dohrenwend BP: Candidate risk factors for temporomandibular pain and dysfunction syndrome: psychosocial, health behavior, physical illness and injury. Pain 1988;34:139–151.
30 Macfarlane TV, Blinkhorn AS, Davies RM, Kincey J, Worthington HV: Association between female hormonal factors and oro-facial pain: study in the community. Pain 2002;97:5–10.
31 LeResche L, Saunders K, Von Korff M, Barlow W, Dworkin SF: Use of exogenous hormones and risk of temporomandibular disorder pain. Pain 1997;69:153–160.
32 Hatch JP, Rugh JD, Sakai S, Saunders MJ: Is the use of exogenous estrogen associated with temporomandibular signs and symptoms? J Am Dent Assoc 2001;132:319–326.
33 Huang GJ, Gansky SA: This study reports no relationship between exogenous estrogen and temporomandibular disorders. J Evid Base Dent Pract 2001;1:191–193.
34 Dao TT, Knight K, Ton-That V: Modulation of myofascial pain by the reproductive hormones: a preliminary report. J Prosthet Dent 1998;79:663–670.
35 LeResche L, Mancl L, Sherman JJ, Gandara B, Dworkin SF: Changes in temporomandibular pain and other symptoms across the menstrual cycle. Pain 2003;106:253–261.
36 Dworkin SF, LeResche L: Research diagnostic criteria for temporomandibular disorders. J Craniomandib Disord Facial Oral Pain 1992;6:301–355.
37 LeResche L, Sherman JJ, Huggins KH, Saunders K, Mancl LA, Lentz G, Dworkin SF: Musculoskeletal orofacial pain and other signs and symptoms of temporomandibular disorders during pregnancy: a prospective study. J Orofac Pain 2005;19:193–201.
38 Sternberg WF, Wachterman MW: Experimental studies of sex-related factors influencing nociceptive responses: nonhuman animal research; in Fillingim RB (ed): Sex, Gender and Pain: Progress in Pain Research and Management. Seattle, IASP Press, 2003, vol 17, pp 71–88.
39 Pisanty S, Rafaely B, Polishuk W: The effect of steroid hormones on buccal mucosa of menopausal women. Oral Surg Oral Med Oral Pathol 1975;40:346–353.

40 Forabosco A, Criscuolo M, Coukos G, Uccelli E, Weinstein R, Spinato S, Botticelli A, Volpe A: Efficacy of hormone replacement therapy in postmenopausal women with oral discomfort. Oral Surg Oral Med Oral Pathol 1992;73:570–574.
41 Wardrop RW, Hailes J, Burger H, Reade PC: Oral discomfort at menopause. Oral Surg Oral Med Oral Pathol 1989;67:535–540.
42 Ferguson MM, Carter J, Boyle P, Hart DM, Lindsay R: Oral complaints related to climacteric symptoms in oophorectomized women. J R Soc Med 1981;74:492–498.
43 Hakeberg M, Berggren U, Hagglin C, Ahlqwist M: Reported burning mouth symptoms among middle-aged and elderly women. Eur J Oral Sci 1997;105:539–543.
44 Tarkkila L, Linna M, Tiitinen A, Lindqvist C, Meurman JH: Oral symptoms at menopause – the role of hormone replacement therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:276–280.
45 Maresky LS, van der Bijl P, Gird I: Burning mouth syndrome: evaluation of multiple variables among 85 patients. Oral Surg Oral Med Oral Pathol 1993;75:303–307.
46 Chen LA, Truelove E, Drangsholt M, Dworkin SF, Sommers E, Benton TS, Mancl L, LeResche L: Hormonal changes and other related factors in atypical facial pain. J Dent Res 2001;80(special issue):84.
47 Yamada K, Nozawa-Inoue K, Kawano Y, Kohno S, Amizuka N, Iwanaga T, Maeda T: Expression of estrogen receptor alpha (ER alpha) in the rat temporomandibular joint. Anat Rec A Discov Mol Cell Evol Biol 2003;274:934–941.
48 Guan G, Kerins CC, Bellinger LL, Kramer PR: Estrogenic effect on swelling and monocytic receptor expression in an arthritic temporomandibular joint model. J Steroid Biochem Mol Biol 2005;97:241–250.
49 Cairns BE, Sim Y, Bereiter DA, Sessle BJ, Hu JW: Influence of sex on reflex jaw muscle activity evoked from the rat temporomandibular joint. Brain Res 2002;957:338–344.
50 Cairns BE, Hu JW, Arendt-Nielsen L, Sessle BJ, Svensson P: Sex-related differences in human pain and rat afferent discharge evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2001;86:782–791.
51 Arthuri MT, Gameiro GH, Tambeli CH, de Arruda Veiga MC: Peripheral effect of a kappa opioid receptor antagonist on nociception evoked by formalin injected in TMJ of pregnant rats. Life Sci 2005;76:1177–1188.
52 Puri V, Cui L, Liverman CS, Roby KF, Klein RM, Welch KM, Berman NE: Ovarian steroids regulate neuropeptides in the trigeminal ganglion. Neuropeptides 2005;39:409–417.
53 Okamoto K, Tashiro A, Hirata H, Bereiter DA: Differential modulation of TMJ neurons in superficial laminae of trigeminal subnucleus caudalis/upper cervical cord junction region of male and cycling female rats by morphine. Pain 2005;114:203–211.
54 Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppe RA, Zubieta JK: Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. J Neurosci 2006;26:5777–5785.
55 Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS: mu-opioid receptor-mediated antinociceptive responses differ in men and women. J Neurosci 2002;22:5100–5107.

Linda LeResche, ScD
Professor
Department of Oral Medicine, University of Washington
Box 356370
Seattle, WA 98195–6370 (USA)
Tel. +1 206 616 6049, Fax +1 206 685 8412, E-Mail leresche@u.washington.edu

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 56–74

Pathophysiology of Orofacial Pain

Barry Sessle

Faculty of Dentistry, University of Toronto, Toronto, Ont., Canada

Abstract

Compared to the limited knowledge base that existed 30 years ago of the pathophysiological processes underlying orofacial pain conditions, several of which are unique to the face and mouth, a great deal has been learnt about these processes in recent years. Recent findings related in particular to peripheral sensitization and central sensitization of orofacial nociceptive processes have provided some important insights into how orofacial pain arises and may become persistent. Nevertheless, there are still critical gaps in our knowledge, and further experimental studies are necessary to fully understand the pathophysiological mechanisms involved in the various types of orofacial pain conditions. Advances in basic and clinical research that clarify these processes will result in improvements in diagnostic and management approaches for these pain conditions in the face and mouth.

The etiology and underlying pathophysiological processes of most acute pain conditions occurring in the face and mouth have undergone considerable investigation in the past 30 years. These are now reasonably well understood, although there are still several points requiring clarification, as outlined in the preceding chapters and reemphasized in the current chapter. However, it is clear from several contributions in this book that the etiology of most of the chronic pain conditions expressed in the orofacial region is unclear, and that their pathogenesis is still unresolved. This chapter will summarize the dogmas and generalizations that developed about these acute and chronic orofacial pain processes, what is currently known of these processes, their clinical implications and future research directions that are essential for further advancement of the field.

Peripheral Processes

Peripheral tissues are innervated by several types of primary afferent nerve fibers that supply various types of sensory organs (receptors) in the tissues. Many of these are small-diameter, slowly conducting afferents (Aδ and C fiber) and it has often been assumed in the past, and still appears in some publications, that all these Aδ and C fiber afferents terminate as free nerve endings that function as nociceptors, i.e. they are activated by noxious stimuli applied to the tissue that they innervate, and that they always give rise to pain. In other words, it is often considered that these afferents exclusively represent the peripheral 'basis' for pain. However, it is now clear that the afferent inputs into the central nervous system (CNS) that are evoked by noxious stimulation may not necessarily produce pain in all instances since, as noted below, there are intrinsic brain mechanisms that can suppress nociceptive transmission to the extent that pain is not elicited by the noxious stimulation. Also, while the free endings of many Aδ and C fiber afferents do function as nociceptors, the endings of some Aδ and C fiber afferents can respond as well or instead to nonnoxious stimuli, e.g. some function as thermoreceptors responsive to cool or warm stimuli. Furthermore, following some tissue injuries, the larger, faster-conducting (Aβ) afferents that supply low-threshold mechanoreceptors responsive to tactile stimuli may become sensitive to noxious stimuli and provide afferent inputs into the CNS that can contribute to certain pain conditions [1–3].

In the case of those nociceptors that are associated with Aδ and C fiber afferents, like nociceptors elsewhere in the body (see the chapters by Mense, pp 7–17, and Schaible, pp 18–27), those in the orofacial region can be activated by intense mechanical, thermal or chemical stimulation of orofacial tissues and thereby detect and encode noxious physical, thermal or chemical events associated with actual or potential tissue damage [1, 4–6]. And like most primary afferents innervating facial cutaneous, intraoral (e.g. mucosa, periodontium, tooth pulp), musculoskeletal and cerebrovascular tissues, the primary afferent cell bodies of these nociceptive afferents occur in the trigeminal ganglion. Studies using in vivo electrophysiological and in vitro recordings as well as molecular and immunocytochemical approaches have shown that trigeminal ganglion cell bodies and their counterparts in the spinal dorsal root ganglia synthesize a vast array of chemicals that help define the role that the primary afferent nociceptive neurons play in encoding pain [7, 8]. These include calcitonin gene-related peptide, substance P, glutamate, somatostatin and nerve growth factor, and the afferents may express serotonergic, cholinergic, opiate, purinergic, bradykinin, histamine, anandamide, prostaglandin or acid-sensitive receptors and ion channels, as well as adrenoreceptors and the capsaicin-sensitive (transient receptor potential vanilloid 1) or -insensitive (transient receptor potential vanilloid 2) receptors.

These various mediators and their action on primary afferent membrane receptors, ion chemicals and intracellular signaling processes have been the subject of much intense study in the spinal somatosensory system, and each of these mechanisms has been implicated in specific processes accounting for the activation or so-called 'peripheral sensitization' (increased excitability) of different subsets of nociceptive afferents to the different types of noxious stimuli [3, 9, 10]. There has been a tendency to conclude that exactly similar peripheral mechanisms apply to orofacial nociceptive processes as those documented for spinal nociceptive processes, and indeed spinal pain scientists and clinicians often overlook orofacial pain mechanisms when considering pain mechanisms in general. However, some of the tissues in the orofacial region (e.g. tooth pulp, periodontium, cornea) are unique to this part of the body, and there are other significant differences between orofacial and spinal sensory systems. These include fundamental differences in the anatomical, physiological and neurochemical profiles of the afferents or their ganglion cell bodies, and their responses to peripheral injury or inflammation (table 1).

The properties of different types of Aδ and C fiber nociceptive afferents supplying the facial skin and oral mucosa have been detailed [1, 5, 8]. There is virtually no information available on the properties of periodontal nociceptive afferents, but considerable attention has been given to the peripheral afferent mechanisms in dentine and pulp. Earlier concepts attributing sensitivity solely to intradentinal or odontoblast transduction mechanisms [for reviews, see 1, 12] have gained little support, with most evidence now favoring a hydrodynamic mechanism underlying the activation of intradental afferents [12–14]. Certainly, tissue injury and inflammation can lead to neurochemical changes and nerve sprouting as well as induce peripheral sensitization of intradental afferents that can result in extremely intense toothache [12–14]. And in other tissues, the changes in afferent sensitivity are due to several different inflammatory mediators and intraneural chemicals, but unlike other tissues, inflammation of the pulp occurs in a noncompliant environment (since it is encased by dentine) with a high extracellular tissue pressure; this may account for the exquisite sensitivity of pulp afferents when the pulp is inflamed. Also, the earlier dogma that pain is the only sensation evoked from the pulp and dentine and that these tissues are supplied only by Aδ and C fiber afferents has been laid to rest. Sensations other than pain may be evoked from intradental tissues, and Aβ afferents comprise a considerable proportion of the sensory innervation of the tooth pulp. Although recent studies suggest dentinal innervation mainly involves A fibers whereas C fiber afferents supply pulpal tissues, further studies are nonetheless needed to clarify the relative contributions of these 3 sets of afferents to pulpal and dentinal pain, the extent to which hydrodynamic mechanisms can account for their activation and the precise role in dental pain of the immune, vascular and neurotrophic factors that have been shown to operate in the pulp.

Table 1. Trigeminal sensory systems: differences from spinal sensory systems

(A) Peripheral tissues and innervation

(1) Tissues unique to the craniofacial region (e.g. tooth pulp, cornea)
(2) Higher innervation density in many craniofacial tissues than in most spinally innervated tissues
(3) Shorter conduction distances of peripheral nerve pathways
(4) Slower conduction velocities of peripheral nerve fibers
(5) Higher ratio of myelinated: unmyelinated fibers
(6) Lower proportion of sympathetic efferents
(7) Certain craniofacial receptors (e.g. some periodontal mechanoreceptors; jaw muscle spindles) have their primary afferent cell bodies *within* the CNS

(B) Central nervous system

(1) Face and mouth represented completely at most rostrocaudal levels of the VBSNC, and a dual representation of some tissues occurs in the Vc
(2) Distinctive brainstem termination patterns of some nociceptive afferents
(3) Transitional regions between Vc and Vi, and between Vc and CDH, with distinctive properties (e.g. bilateral afferent inputs to Vc/Vi)
(4) 'Deep bundle' fiber system especially prominent in the Vc (connects caudal and rostral levels of the VBSNC), whereas Lissauer's tract is absent
(5) Significant ipsilateral as well as contralateral projections from VBSNC to thalamus

(C) Pain conditions specific to the craniofacial region

(1) Headaches (e.g. migraine, cluster headache)
(2) Toothaches (e.g. pulpitis pain)
(3) Trigeminal neuralgia
(4) Miscellaneous (e.g. persistent idiopathic facial pain, atypical odontalgia, burning mouth syndrome)

CDH = Upper cervical dorsal horn; VBSNC = trigeminal brainstem sensory nuclear complex; Vc = subnucleus caudalis; Vi = subnucleus interpolaris. From Sessle [11], with permission.

Studies of the mechanisms underlying the activation and sensitization of afferents supplying musculoskeletal tissues [e.g. temporomandibular joint (TMJ), muscle] and dural or cranial vessels, while limited in number, have nonetheless recently revealed some intriguing features of these processes that warrant further investigations. These afferents can be activated or modulated by peripherally acting chemical mediators long thought to have actions on neurons within the CNS. These include serotonin, excitatory amino acids (e.g. glutamate), opioids and γ-aminobutyric acid receptor mechanisms that have been implicated in several orofacial pain conditions (e.g. pulpitis, TMJ arthralgia, headache, myofascial pain) [15–18]. Furthermore, sex differences occur in the peripheral actions of chemicals (e.g. glutamate, morphine) that operate through

some of these receptor mechanisms [8, 19, 20]. These findings raise the possibility that peripherally based physiological mechanisms may contribute to the sex differences in the prevalence of many chronic pain orofacial conditions. Further studies are thus warranted in humans as well as animals to examine further the possible role in these sex differences of peripheral mechanisms in afferents supplying these and other orofacial tissues.

There are additional clinical implications and future research directions stemming from these findings of various processes involved in the activation or peripheral sensitization of nociceptive orofacial afferents. One is that they represent important factors in many painful conditions that clinicians are called upon to treat, such as arthritis, pulpitis and mucositis. The chemical mediators released as part of the peripheral sensitization process may also diffuse through the peripheral tissues and act on the endings of adjacent nociceptive afferents and so contribute to the spread of the painful area. In addition, since peripheral sensitization of nociceptive afferent endings at the injury site is reflected in an increased excitability of the endings, the afferent endings may manifest spontaneous activity, a decreased activation threshold and increased responsiveness to subsequent stimulation of the site of the endings. These changes may contribute, respectively, to the spontaneous pain, allodynia and hyperalgesia that are features of many acute as well as chronic or persistent pain conditions. The increased afferent barrage into the CNS from this increased nociceptor activity may also lead to functional changes in central nociceptive processing that contribute to persistent pain, e.g. central sensitization (see below).

Furthermore, the action of many common peripherally based pain management approaches can be explained by their influence on these mechanisms. For example, local anesthetics are effective in blocking nerves and eliminating pain from peripheral tissues because they interfere with the ionic channels and currents involved in the initiation and conduction of action potentials along nociceptive afferents into the CNS. Also, many common nonsteroidal anti-inflammatory drugs as well as several more recently developed analgesics (e.g. cyclooxygenase 2 inhibitors) have their principal anti-inflammatory or analgesic actions in peripheral tissues. By reducing inflammation associated with tissue injury and by modulating the excitability of nociceptive afferents, they can reduce the hyperalgesia associated with short-term orofacial pain conditions.

In addition, the large variety of peripheral mediators and mechanisms discovered in recent years emphasizes the complexity of the peripheral processes involved in pain. Nonetheless, the identification of the many peripheral factors and the clarification of their mechanisms of action provide new opportunities to control pain since the multiplicity of peripheral chemical mediators involved in peripheral nociceptive activation, sensitization and related events (e.g. inflammation) are all potential targets for the development of new and more effective

therapeutic approaches to pain control [3, 9, 10] without the undesirable side effects that characterize many centrally acting analgesics that are currently in use.

The recent findings also emphasize that earlier concepts that afferents and their ganglion cell bodies are relatively simple conduits into the CNS for signals arising from peripheral sense organs are too simplistic a view. The afferent endings and their axons and ganglion cell bodies are subject to considerable modulation and modification by the various factors mentioned above. Recent studies clearly reveal that a peripheral substrate exists for complex interactions between the neural, immune, cardiovascular and endocrine systems. There may also be cross-talk and interactions between adjacent afferents or ganglion neurons, and these features may be enhanced following peripheral tissue or nerve injury or inflammation [21, 22]. This can lead to ectopic firing of afferent inputs into the CNS that could contribute to the development of a chronic pain state. Additional changes in peripheral afferents that have been discovered in animal models of chronic neuropathic and inflammatory pain include other types of abnormal firing of nociceptive afferents, phenotypic changes in the afferent endings or their ganglion cell bodies, sprouting of their central endings in the CNS and enhanced sympathetic modulation of nociceptive afferents [3, 22, 23]. However, not all these various changes have been demonstrated or even explored in orofacial pain models, and an important future direction is to determine whether these mechanisms exist in animal models developed specifically to mimic orofacial pain conditions and to what extent they may contribute to each of these conditions. Future investigations should also address possible biomarkers and genetic and environmental influences in these peripheral orofacial nociceptive mechanisms so as to give better mechanistic insights and improved diagnostic approaches for the different types of orofacial pain conditions.

Brainstem Nociceptive Processes

The trigeminal brainstem sensory nuclear complex (VBSNC) is the projection site of most orofacial primary afferents. Its second-order neurons project directly or indirectly to the thalamus and to several brainstem areas (e.g. parabrachial nucleus, cranial nerve motor nuclei, reticular formation), and also contribute to intrinsic projections terminating within the complex itself. The VBSNC consists of the main sensory nucleus and the spinal tract nucleus, and the latter is subdivided into 3 subnuclei: oralis, interpolaris and caudalis. The subnucleus caudalis has several morphological and physiological similarities with the spinal dorsal horn, to the extent that it is now often termed the medullary dorsal horn [1, 5, 11, 19]. For example, like the spinal dorsal horn

that plays such a crucial role in spinal nociceptive processing, the subnucleus caudalis is a laminated structure; this includes a substantia gelatinosa which generally has similar features to that of the spinal dorsal horn. In addition, whereas the large mechanosensitive primary afferents that supply orofacial tissues terminate throughout the VBSNC, including laminae III/IV of the subnucleus caudalis, the small myelinated or unmyelinated primary afferents end almost exclusively in the subnucleus caudalis (most densely in its laminae I–II) [5, 6, 11, 19]. These small-diameter afferents include nociceptive afferents, and some stain positive for substance P, calcitonin gene-related peptide and neurotrophins, others stain negative for the neuropeptides but positive for the cell surface marker isolectin B_4; these isolectin B_4 afferents have a different distribution in the subnucleus caudalis compared with the spinal dorsal horn [24]. Furthermore, several receptor types associated with nociceptive processing or its modulation are localized in the caudalis endings of these different types of afferents, or in the neurons in the subnucleus caudalis, e.g. neurokinin, opiate, γ-aminobutyric acid, purinergic, transient receptor potential vanilloid 1, estrogen and glutamatergic (N-methyl-D-aspartate, NMDA, and non-NMDA) receptors.

Like the spinal dorsal horn, the subnucleus caudalis also has two classes of nociceptive neurons, based on their cutaneous (or mucosal) mechanoreceptive field (RF) and response properties, in its superficial and deep laminae: high-threshold or nociceptive-specific (NS) neurons and wide dynamic range (WDR) neurons. NS neurons receive small-diameter nociceptive afferent inputs, and WDR neurons receive both large- and small-diameter inputs. Low-threshold mechanoreceptive (LTM) neurons and thermoreceptive neurons also occur in the subnucleus caudalis, as in the spinal dorsal horn, and likely contribute to orofacial tactile and thermal sensibilities. In contrast, the NS and WDR neurons with a cutaneous RF play an important role in our ability to localize, detect and discriminate cutaneous and mucosal noxious stimuli [5, 19]. The majority of the caudalis NS and WDR neurons can nonetheless also be excited by afferents from deep tissues (e.g. tooth pulp, cerebrovasculature, TMJ, masticatory muscle) as well as by cutaneous or mucosal afferent inputs, and there are sex differences in some of these responses [19, 25, 26]. Such features are thought to contribute to central sensitization and referred pain and possibly to the sex differences in some orofacial pain conditions (see below).

The structural and functional similarities between the subnucleus caudalis and the spinal dorsal horn have shaped discussions of the special involvement of this subnucleus in orofacial pain [6, 11, 19]. However, this useful homology needs revision since several differences exist between subnucleus caudalis and spinal dorsal horn, and indeed other differences occur in the trigeminal and spinal central processes (table 1). Recent evidence indicates that certain parts of

the subnucleus caudalis are organized differently from the spinal system. As mentioned above, a unique feature of the trigeminal somatosensory system is the processing of nociceptive inputs from afferents supplying structures not found elsewhere in the body; these include the tooth pulp, periodontal tissues, cornea and nasal mucosa. While these inputs are mainly processed in the subnucleus caudalis, another unique feature of the caudalis is its dual representation of several orofacial tissues in its rostral and caudal portions. The caudal part of the subnucleus merges without clear boundaries with the cervical dorsal horn, while the rostral part of the caudalis forms a distinctive transition region with the subnucleus interpolaris. This transition region has a dorsomedial transition area and a ventral transition area, which is especially clear in rodents, and receives bilateral afferent inputs from orofacial tissues. It is becoming apparent that these two areas of the rostral caudalis, and the caudal part of the caudalis, have each their own unique morphological and functional features that may be differentially involved in perceptual, autonomic, endocrine and muscle reflex responses to noxious stimulation of certain orofacial tissues [24, 27]. Further investigation of these different areas within and adjacent to the caudalis should shed light on their specific functional roles in orofacial nociceptive mechanisms.

Another long-held concept that the caudalis is *the* crucial element in the VBSNC for the relay of orofacial nociceptive signals also no longer rings true [for reviews, see 1, 11, 19, 24]. Some orofacial nociceptive behaviors may persist after caudalis lesions, lesions of the rostral components (e.g. subnucleus oralis) of the VBSNC may disrupt some pain behaviors, the rostral components have substantial numbers of NS and WDR neurons with an intraoral or perioral nociceptive RF (including tooth pulp), and the rostral components contribute to ascending and reflex nociceptive pathways and also manifest some neurochemical markers for nociceptive processes [19, 28]. While recent studies indicate that some of the response properties of rostral nociceptive neurons, particularly in the subnucleus oralis, may be dependent on more caudal regions such as the subnucleus caudalis for the relay of nociceptive signals (also see below), the relative roles of the rostral and caudal components of the VBSNC in nociceptive responses to noxious stimulation of cutaneous and deep craniofacial tissues and tooth pulp represent an important subject that requires more research attention.

There are other research avenues that also require more emphasis. These include the need to provide more details on the neurochemical and molecular markers of nociceptive afferents supplying specific orofacial tissues and on their termination patterns in the different components of the VBSNC, the cellular and molecular processes involved in nociceptive transmission in these different components, and whether sex differences occur in any of these various features that might contribute to the sex differences in orofacial pain.

Some clinical implications of these various findings also should be noted. Firstly, the spatial and temporal coding features of caudalis nociceptive neurons, especially those that respond only to cutaneous (or oral mucosal) noxious stimuli and project to higher brain areas involved in perception, indicate that the subnucleus caudalis is a crucial brainstem structure underlying our ability to perceive and localize acute superficial pain and to sense its intensity and duration. Nonetheless, as noted above, nociceptive circuits involving the rostral components of the VBSNC also appear to contribute to brainstem reflex circuits as well as to the perceptual and other pain behaviors that depend on higher brain center function. Thus, several pathways operating through more than one component of the VBSNC are likely operational in patients with acute or chronic orofacial pain.

Secondly, sex hormone receptors exist in the VBSNC, and there are sex differences in the responsiveness of caudalis nociceptive neurons to deep afferent inputs (see above). Together with the sex differences documented for the responsiveness of some nociceptive primary afferents, it is possible that these differences may contribute to the sex differences documented for many orofacial pain conditions. As noted above, attention to possible differences in males and females is needed in future studies of VBSNC nociceptive processes.

Thirdly, a notable feature of caudalis NS and WDR neurons is the convergence onto the majority of them of afferent inputs from musculoskeletal (e.g. TMJ, muscle), tooth pulp and cranial vessels and dura as well as from cutaneous or mucosal tissues. Many of these nociceptive neurons also receive afferent inputs from other cranial nerves or cervical nerves. These convergence patterns, together with a process termed central sensitization (see below), have been implicated in the diffuse and referred pain within and between the head and neck that is a feature of many orofacial pain conditions [e.g. temporomandibular disorders (TMDs), toothache or headache] [16, 17, 19].

Thalamocortical Nociceptive Processes

The signals from the VBSNC are relayed to higher levels of the CNS and in particular to the thalamus and from there to the cerebral cortex [29, 30]. The thalamus receives direct contralateral and some ipsilateral input from the VBSNC. Many LTM neurons and some thermoreceptive neurons occur especially in the ventroposterior medial thalamic nucleus and are involved in transmitting tactile and thermosensitive information to the cerebral cortex. The ventroposterior medial thalamic nucleus also contains NS and WDR neurons, and these nociceptive neurons generally have properties similar to those described for NS and WDR neurons in the VBSNC, including convergence of

cutaneous and deep afferent inputs. Their RF and response properties and their connections with the overlying somatosensory cerebral cortex suggest that most are involved in the sensory-discriminative dimension of pain (i.e. pain localization and intensity discrimination). Nociceptive neurons receiving orofacial inputs also occur in other thalamic areas (e.g. medial nuclei and nucleus submedius) but are usually considered to be involved more in the affective or motivational dimensions of pain.

The main cortical targets of the thalamic nuclei receiving nociceptive inputs are the primary and secondary somatosensory cortices, the insula and the cingulate. A limited number of studies have documented NS and WDR neurons in the primary face somatosensory cerebral cortex. These nociceptive neurons respond to noxious facial or tooth pulp stimuli in a manner suggesting a role in the sensory-discriminative dimension of pain. Nociceptive neurons also occur in other cortical regions such as the anterior cingulate cortex which has been implicated in the affective or motivational dimension of pain [31, 32]. Imaging studies in humans also support these findings, but very few imaging or electrophysiological studies have been directed at thalamocortical processes underlying specifically orofacial pain. Along with the almost complete lack of any studies of the neurochemical processes at these levels underlying orofacial pain, a major gap in understanding exists of the higher brain processing related to acute or chronic orofacial pain.

Nociceptive Reflex and Behavioral Responses

As well as projecting to thalamocortical regions involved in sensory-discriminative, cognitive, effective or motivational aspects of pain perception, many neurons in the VBSNC relay to the brainstem or other brain centers involved in reflex or other behavioral responses to noxious orofacial stimuli. Orofacial pain can be associated with reflex changes in blood pressure, heart rate, breathing and salivation evoked by noxious orofacial stimulation. There is also a close interplay between sensory and motor pathways in pain, and many studies in animals and humans have detailed the reflex effects on muscle activity of various types of orofacial noxious stimuli [11, 33]. These include the classical jaw-opening reflex that may be accompanied by inhibitory ('silent') periods in the jaw-closing musculature. Earlier studies had claimed that these silent periods were of diagnostic, even prognostic, significance in conditions (e.g. TMDs) reflecting neuromuscular dysfunction in the orofacial region, but this has not been borne out by better-controlled experimental studies in humans. Much attention has also been given to effects of noxious stimuli on postural jaw muscle activity, since increases in electromyographic (EMG)

activity induced by pain have been conceived as being of clinical importance in the pathophysiological mechanisms underlying many musculoskeletal disorders manifesting pain, such as TMD and tension-type headaches. There is, however, no consensus on whether the EMG activity of jaw muscles increases, decreases or remains unchanged during orofacial pain, and a number of factors have been invoked as accounting for the disparity in experimental and clinical pain data [33, 34]. In those studies where an increase in jaw EMG activity has been reported in humans, its relatively small magnitude suggests that it may have little clinical significance. The human findings however contrast with the robust and prolonged jaw EMG increases reflexly induced in the jaw-opening and jaw-closing muscles by algesic stimuli applied to the TMJ and other orofacial tissues in animals; the reflex circuitry to the α-motoneurons in the trigeminal motor nucleus supplying these muscles involves interneurons in the subnucleus caudalis [11, 19]. These data indicate that excitatory reflex pathways do indeed exist from peripheral orofacial nociceptors and suggest that the cocontraction of the jaw muscles may provide a 'splinting' effect that limits jaw movements in pathophysiological conditions affecting deep tissues such as the TMJ and muscle.

These and other findings also bear on current and long-held concepts related to the etiological factors and pathophysiological processes involved in TMD pain, especially the so-called vicious cycle theory that muscle hyperactivity leads to pain which leads to more muscle hyperactivity and so on. Heavy muscle exercise does appear to lead to microtrauma in muscles and connective tissue which is usually followed by pain that peaks in about 24 h (i.e. postexercise muscle soreness); however, it is unclear whether such processes characterize TMD pain. Furthermore, most elements of the vicious cycle have not been experimentally tested or proven, and instead a concept of pain adaptation has been proposed on the basis of findings in animals and humans. This concept proposes that pain may lead to agonist muscles becoming less active during a movement (e.g. the masseter muscle during jaw-closing phases of mastication) and antagonist muscles (e.g. anterior digastric) becoming more active in this movement, and that this limits jaw mobility and may aid healing [34]. While this model has many attractive features, further studies are called for to test the applicability of this model to various experimental and clinical pain conditions, including chronic orofacial pain states. Studies are also needed to define the effects of orofacial noxious stimuli on higher-center processes involved in jaw motor control and on the function of other muscle groups (e.g. tongue, facial musculature). Since there has only been limited study of these effects and the data appear conflicting [35], more detailed investigation is also needed to elucidate further the effects of psychological state (e.g. emotion, depression, anxiety), sleep and wakefulness on these processes [36]. The clinical significance of

such studies lies not only in their helping to elucidate the reported neuromuscular dysfunction or neuromuscular adjustments that may accompany orofacial pain states, but also the mechanisms and sensorimotor linkages that may be involved in different psychological, physiological and pathophysiological states such as oral dyskinesias and bruxism.

Modulatory Influences and Mechanisms

Modulatory Effects and Pathways

Earlier concepts of pain and its underlying processes provided a narrow perspective of pain, looking upon it as a simple sensation closely tied to the intensity of the peripheral stimulus. However, pain is now conceptualized as a multidimensional sensory experience that is very much subject to modification by other ongoing sensory experiences, psychological factors etc. Several brain areas can modify the perceptual, emotional, motivational, cognitive, autonomic and endocrine responses to noxious stimuli, and these modulatory effects may vary from one individual to another. Such variability can explain why pain is a highly personal experience that can be affected by numerous biological, pharmacological, psychological, genetic and environmental influences.

Modulation of the nociceptive transmission process can occur at thalamic and cortical levels, but little attention has been given to orofacial pain-modulatory mechanisms at these higher brain levels. Rather, the focus has been on modulatory influences on brainstem nociceptive processing, since the intricate organization of the VBSNC and its variety of inputs from peripheral tissues and from different parts of the brain provide a particularly important substrate for numerous interactions between the various inputs. NS and WDR neurons in the subnucleus caudalis and other components of the VBSNC are subject to modulatory influences originating locally within the subnucleus caudalis or in more rostral parts of the VBSNC as well as descending modulatory influences stemming from the brainstem and higher brain centers. Often overlooked are findings that many of these modulatory influences target nonnociceptive neurons (e.g. LTM) as well as nociceptive neurons, so these influences are not all selective for nociceptive transmission. For example, electrical or chemical stimulation of the periaqueductal gray matter or rostral ventromedial medulla/nucleus raphe magnus activates descending pathways that project to the VBSNC and that can modulate trigeminal brainstem neuronal and related reflex and behavioral responses to nonnoxious as well as noxious orofacial stimulation in experimental animals. Other powerful modulatory effects include pathways emanating from the locus coeruleus, pontine parabrachial area, anterior pretectal nucleus, thalamic nucleus submedius as well as the cerebral

cortex (e.g. somatosensory and motor areas) [1, 19, 27, 37]. These descending pathways exert their effects by the release of certain neurochemicals (e.g. serotonin) from their endings within the VBSNC or by their causing other neurochemicals (e.g. enkephalins, γ-aminobutyric acid) to be released from the endings of interneurons intrinsic to the VBSNC (e.g. in the substantia gelatinosa of the subnucleus caudalis).

The pathways and chemical processes that can inhibit the activity of nociceptive neurons in the subnucleus caudalis or other parts of the VBSNC are likely involved in several approaches that have been reported to reduce pain, such as deep brain stimulation, cortical stimulation and placebo, and may also be modulated by attention and distraction, sleep/wake or emotional state, and can be up- or downregulated in pain states [27, 37]. While many of these descending influences are inhibitory and thus contribute to mechanisms underlying analgesia, some can exert facilitatory effects and so be involved in the augmentation of pain that may occur in states of anxiety or emotion (also see below). In addition, descending inhibitory influences on nociceptive neurons have been implicated as intrinsic mechanisms contributing to the analgesic effects reported for acupuncture and for opiate-related and serotonin agonist drugs such as morphine and serotonin reuptake inhibitors, respectively. Furthermore, noxious stimulation of one part of the body can induce a powerful suppression of transmission of nociceptive signals elicited from another part of the body, so-called diffuse noxious inhibitory controls. It is likely that these or analogous afferent-induced mechanisms could also contribute to the reported analgesic efficacy of counterirritation and some forms of acupuncture and transcutaneous electrical nerve stimulation. However, the evidence basis of the efficacy of many of these approaches is still limited, and more research in this area is needed. Nonetheless, modulatory influences and mechanisms that have been revealed do hold out promise of the development of new therapeutic approaches targeting these mechanisms, and also improve our understanding of how a number of approaches currently in use to manage pain may operate. The neurochemical and molecular processes also need more attention in order to improve upon and expand current therapeutic approaches to manage acute and chronic orofacial pain. Further studies are also needed to define the modulatory mechanisms taking place at thalamic and cortical levels and their relative contribution vis-à-vis brainstem modulation to orofacial pain control. These mechanisms also need more elucidation in relation to chronic as well as acute pain states, since only limited details are available of their role in chronic orofacial pain models.

Central Sensitization

Nociceptive transmission in the trigeminal and spinal sensory systems can also be enhanced by alterations to the peripheral afferent inputs to the CNS that

may result from inflammation or trauma of peripheral tissues and nerves. This emphasizes the plasticity of the neural circuitry underlying nociceptive transmission, i.e. that it is not 'hard-wired' like many early and even some contemporary concepts have depicted. Plasticity in brainstem and higher centers (e.g. somatosensory cortex) of the trigeminal system is not limited to nociceptive neurons, but can also occur in LTM neurons following damage to peripheral nerves.

Plasticity reflected in an enhancement of excitability of nociceptive neurons has been termed 'central sensitization', and damage or inflammation of deep musculoskeletal tissues (e.g. TMJ, masticatory muscle) and tooth pulp is especially effective in inducing central sensitization in the VBSNC. This increased excitability has been documented in NS and WDR neurons in the subnucleus caudalis where it is reflected in an increase in spontaneous activity, lowering of activation threshold, RF expansion and enhancement of peripherally evoked responses of the caudalis nociceptive neurons [19, 28, 38]. These physiological neuronal changes may also be associated with changes in intracellular markers (e.g. c-*fos*) as well as by increased EMG activity in the jaw-opening and jaw-closing muscles, autonomic influences and nociceptive behavior reflecting allodynia and hyperalgesia [19, 22, 27]. The neuronal changes and their underlying neurochemical processes appear to be analogous in general to the central sensitization described in spinal nociceptive pathways which is thought to contribute to persistent pain and its common characteristics of spontaneous pain, allodynia and hyperalgesia, and pain spread and referral. Indeed, several membrane receptor mechanisms, ion channels and intracellular signaling processes are involved in caudalis central sensitization, and include purinergic and neurokinin as well as NMDA and non-NMDA glutamatergic receptor mechanisms [19, 27, 38]. Recent findings suggest that nonneural cells (glia) may also be involved in its development and maintenance [39], and the roles of glia in this process represent a research avenue that is likely to provide important new insights into acute and chronic orofacial pain mechanisms. Moreover, changes in the descending facilitatory and inhibitory influences mentioned above may also contribute to the expression of central sensitization, e.g. central depressive influences (e.g. opioid-related) can normally be 'triggered' by noxious orofacial stimulation and may serve to limit the sensitization. The intracellular processes, messenger systems and membrane receptor and ion channels involved in central sensitization represent an intense area of current research.

It is also noteworthy that trigeminal central sensitization is not limited to the subnucleus caudalis. Central sensitization has also been shown in nociceptive neurons in the subnucleus oralis and in higher brain regions such as the ventroposterior medial thalamus, although the subnucleus caudalis is responsible for their expression of central sensitization by way of its projections to both structures [38].

The discovery of central sensitization and its underlying neuroplastic processes has been an important advance in understanding mechanisms contributing to acute and especially chronic pain states. But central sensitization seems to be a normal physiological consequence of peripheral tissue injury or inflammation, and is usually reversible. An important question then is what are the factors that lead to its maintenance and provide the substrate for a chronic pain state. Much more research is needed on its neurochemical and molecular substrate and intracellular signaling processes, with the view of enhancing our understanding of the pathogenesis of chronic orofacial pain states and improving current management approaches.

While there is agreement that nociceptive afferent inputs related to peripheral tissue injury or inflammation are crucial for the development of central sensitization, their importance in its maintenance is still a matter of conjecture. The resolution of this matter is important since it bears on whether clinical approaches that target peripheral versus central mechanisms are likely to be beneficial or not in managing pain. The dependence of central sensitization on peripheral inputs for its development supports the incorporation into clinical practices of approaches that reduce nociceptive afferent inputs into the CNS and thus reduce the risk for its development and for postoperative pain. Several studies have been carried out in experimental animals and humans to determine if preemptive analgesia (e.g. by local anesthesia) would be effective in reducing postoperative pain, but results have been mixed. A number of factors have been identified that may account for the variability in efficacy, including the likelihood that nociceptive afferent inputs can soon become operational after the local anesthetic block has worn off and then induce a central sensitization and an exaggerated pain state. This would argue for the clinical benefit of instituting adequate postoperative as well as preoperative pain control measures to ensure that central sensitization is minimized.

Another clinical correlate of central sensitization is that most orofacial pain conditions are likely to involve this process to some degree, and peripheral sensitization may also be a factor in many of these conditions. For example, the acute pain and sensitivity of injured orofacial tissue, such as that of a 'hot tooth' that gives an exaggerated response to mechanical or thermal stimuli applied to the inflamed tooth, can be explained by the increased excitability of peripheral nociceptors and central nociceptive neurons associated with peripheral and central sensitization. Likewise, the pain and limitations in jaw movements that are characteristic of TMDs may result from these sensitization phenomena producing states of allodynia and hyperalgesia as well as the changes in jaw-opening and jaw-closing muscle activity noted above. In addition, the presence of a superficial as well as a deep RF in most caudalis nociceptive neurons plus the efficacy of deep nociceptive afferent inputs in inducing caudalis central sensitization

(see above) that includes an expansion of both cutaneous and deep RFs represent neuronal features thought to contribute to the poor localization and referral of deep pain that is a feature of TMDs. Comparable processes have also been implicated in the pain and allodynia of other pain conditions such as migraine headache [17].

Sensitization phenomena, in particular central sensitization, may indeed represent core features in the etiology and pathogenesis of most chronic pain conditions manifested in the orofacial region. For several of these conditions, nerve damage or changes in neural function have been implicated in their etiology, e.g. trigeminal neuralgia, atypical facial pain, atypical odontalgia and burning mouth syndrome. Studies of the past 2 decades have revealed that damage to afferent fibers or deafferentation may trigger several different mechanisms. These include sprouting of the afferents into peripheral tissues and even neuroma formation, the initiation of abnormal impulses in the injured afferents, the development of functional contacts between sympathetic efferents and nociceptive afferents, phenotypic changes in the afferents, structural reorganization and central sprouting of the endings in the CNS of primary afferents, changes in central inhibitory or facilitatory influences and, most recently, changes in glial cell function in the CNS. Most if not all of these processes result in central sensitization of nociceptive processes [11, 19]. Although the study of these changes in trigeminal nociceptive pathways has been much more limited than in spinal nociceptive pathways, recent approaches using nerve injury, or chronic as well as acute inflammation of orofacial tissues, have revealed several comparable physiological and neurochemical changes in trigeminal nociceptive processing in association with exaggerated orofacial pain behavior [19, 22, 27]. It is also important to keep in mind that these pathophysiological processes are undoubtedly themselves modulated by factors related to behavioral and cognitive state and genetic and environmental factors, and thus account why pain is a multidimensional experience, the expression of which can vary from one person to another.

A particular challenge to the orofacial pain field is to clarify which of these various changes are specifically applicable to each of the chronic orofacial pain conditions noted above. Inherent in this challenge is the need for a greater emphasis on the development of animal models to help improve our understanding of the etiology and pathogenesis of these conditions. Many of the current concepts of orofacial pain mechanisms draw largely upon findings from spinal models of chronic pain. Given the uniqueness of some of the orofacial pain conditions (e.g. trigeminal neuralgia, burning mouth syndrome) and the unique features of some of the peripheral and central orofacial sensory mechanisms noted above, there is a need to apply and test these concepts within the framework of the trigeminal system by utilizing chronic orofacial pain models.

The use of emerging technologies related to biological markers, gene expression and molecular biology is also likely to be very important in elucidating the pathophysiology of these conditions.

Conclusion

Three decades ago, little was known of the pathophysiological processes underlying orofacial pain. However, much information has been gained in recent years of peripheral orofacial nociceptive mechanisms and of the representation and processing of orofacial nociceptive inputs in the VBSNC and higher levels of the CNS. Recent findings related to peripheral sensitization and central sensitization have provided some important insights into how orofacial pain arises and may become persistent. Nonetheless important gaps still remain in our knowledge of these processes, and further experimental studies are necessary to fully understand the mechanisms underlying the normal and pathophysiological processing of nociceptive information from the orofacial region. Improvements in diagnostic and management approaches for the persistent pain conditions in the face and mouth will rely heavily on advances in basic and clinical research that clarify these underlying mechanisms.

Acknowledgements

Studies of the author were supported by grants DE04786 and DE15420 of the US National Institute of Dental and Craniofacial Research. The author is the recipient of a Canada Research Chair.

References

1 Dubner R, Sessle BJ, Storey AT: The Neural Basis of Oral and Facial Function. New York, Plenum Press, 1978.
2 Matthews B, Sessle BJ: Peripheral mechanisms of orofacial pain; in Lund JP, Lavigne GL, Dubner R, Sessle BJ (eds): Orofacial Pain: From Basic Science to Clinical Management. Chicago, Quintessence, 2001, pp 37–46.
3 Campbell JN, Meyer RA: Neuropathic pain: from the nociceptor to the patient; in Merskey H, Loeser JD, Dubner R (eds): The Paths of Pain 1975–2005. Seattle, IASP Press, 2005, pp 229–242.
4 Darian-Smith I: Neural mechanisms of facial sensation. Int Rev Neurobiol 1966;9:301–395.
5 Dubner R: Recent advances in our understanding of pain; in Klineberg I, Sessle BJ (eds): Oro-Facial Pain and Neuromuscular Dysfunction: Mechanisms and Clinical Correlates. Oxford, Pergamon Press, 1985, pp 3–19.
6 Dostrovsky JO, Sessle BJ: Nociceptive processing in the brainstem; in Schmidt RF, Willis WD (eds): Encyclopedic Reference of Pain. Heidelberg, Springer, 2006.

7 Gold MS: Molecular basis of receptors; in Merskey H, Loeser JD, Dubner R (eds): The Paths of Pain 1975–2005. Seattle, IASP Press, 2005, pp 49–67.
8 Cooper B: Nociceptors in the orofacial region: skin/mucosa; in Schmidt RF, Willis WD (eds): Encyclopedic Reference of Pain. Heidelberg, Springer, 2006.
9 Julius D: The molecular biology of thermosensation; in Dostrovsky JO, Carr DB, Koltzenburg M (eds): Proceedings of the 10th World Congress on Pain: Progress in Pain Research and Management. Seattle, IASP Press, 2002, vol 24, pp 345–354.
10 Dray A: Future pharmacologic management of neuropathic pain. J Orofac Pain 2004;18:381–385.
11 Sessle BJ: Orofacial pain; in Merskey H, Loeser JD, Dubner R (eds): The Paths of Pain 1975–2005. Seattle, IASP Press, 2005, pp 131–150.
12 Hu JW: Tooth pulp; in Miles TS, Nauntofte B, Svensson P (eds): Clinical Oral Physiology. Copenhagen, Quintessence, 2004, pp 141–163.
13 Byers MR, Närhi MVO: Dental injury models: experimental tools for understanding neuroinflammatory interactions and polymodal nociceptor functions. Crit Rev Oral Biol Med 1999;10:4–39.
14 Narhi MVO: Nociceptors in the dental pulp; in Schmidt RF, Willis WD (eds): Encyclopedic Reference of Pain. Heidelberg, Springer, 2006.
15 Kopp S: Neuroendocrine, immune, and local responses related to temporomandibular disorders. J Orofac Pain 2001;15:9–28.
16 Hargreaves KM, Goodis HE (eds): Seltzer and Bender's Dental Pulp. Chicago, Quintessence, 2002, p 500.
17 Burstein R, Levy D, Jakubowsky M: A thirty-year perspective on the pathophysiology of migraine pain; in Merskey H, Loeser JD, Dubner R (eds): The Paths of Pain 1975–2005. Seattle, IASP Press, 2005, pp 151–164.
18 Lam DK, Sessle BJ, Cairns BE, Hu JW: Neural mechanisms of temporomandibular joint and masticatory muscle pain: a possible role for peripheral glutamate receptor mechanisms. Pain Res Manag 2005;10:145–152.
19 Sessle BJ: Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. Crit Rev Oral Biol Med 2000;11:57–91.
20 Cairns B: Nociceptors in the orofacial region: TMJ and muscle; in Schmidt RF, Willis WD (eds): Encyclopedic Reference of Pain. Heidelberg, Springer, 2006.
21 Devor M, Amir R, Rappaport ZH: Pathophysiology of trigeminal neuralgia: the ignition hypothesis. Clin J Pain 2002;18:4–13.
22 Iwata K, Tsuboi Y, Shima A, Harada T, Ren K, Kanda K, Kitagawa J: Central neuronal changes after nerve injury: neuroplastic influences of injury and aging. J Orofac Pain 2004;18:293–298.
23 Robinson PP, Boissonade FM, Loescher AR, Smith KG, Yates JM, Elcock C, Bird EV, Davies SL, Smith PL, Vora AR: Peripheral mechanisms for the initiation of pain following trigeminal nerve injury. J Orofac Pain 2004;18:287–292.
24 Bereiter DA, Hiraba H, Hu JW: Trigeminal subnucleus caudalis beyond homologies with the spinal dorsal horn. Pain 2000;88:221–224.
25 Dostrovsky JO, Davis KD, Kawakita K: Central mechanisms of vascular headaches. Can J Physiol Pharmacol 1991;69:652–658.
26 Okamoto K, Hirata H, Takeshita S, Bereiter DA: Response properties of TMJ neurons in superficial laminae at the spinomedullary junction of female rats vary over the estrous cycle. J Neurophysiol 2003;89:1467–1477.
27 Dubner R, Ren K: Brainstem mechanisms of persistent pain following injury. J Orofac Pain 2004;18:299–305.
28 Woda A: Pain in the trigeminal system: from orofacial nociception to neural network modeling. J Dent Res 2003;82:764–768.
29 Dostrovsky JO, Craig AD: Ascending projection systems; in McMahon SB, Koltzenburg M (eds): Textbook of Pain, ed 5. London, Elsevier, 2006, pp 187–203.
30 Shigenaga Y, Yoshida A: Trigeminal brainstem nuclear complex anatomy; in Schmidt RF, Willis WD (eds): Encyclopedic Reference of Pain. Heidelberg, Springer, 2006.
31 Bushnell MC: Brain imaging of pain: a thirty-year perspective; in Merskey H, Loeser JD, Dubner R (eds): The Paths of Pain 1975–2005. Seattle, IASP Press, 2005, pp 285–297.

32 Iwata K, Tsuboi Y, Tashiro A, Sakamoto M, Sumino R: Integration of tooth-pulp pain at the level of cerebral cortex; in Nakamura Y, Sessle BJ (eds): Neurobiology of Mastication – From Molecular to Systems Approach. Tokyo, Elsevier, 1999, pp 471–481.
33 Svensson P, Graven-Nielsen T: Craniofacial muscle pain: review of mechanisms and clinical manifestations. J Orofac Pain 2001;15:117–145.
34 Lund JP: Pain and movement; in Lund JP, Lavigne GJ, Dubner R, Sessle BJ (eds): Orofacial Pain: From Basic Science to Clinical Management. Chicago, Quintessence, 2001, pp 151–163.
35 Halkjaer L, Melsen B, McMillan AS, Svensson P: Influence of sensory deprivation and perturbation of trigeminal afferent fibers on corticomotor control of human tongue musculature. Exp Brain Res 2006;170:199–205.
36 Lavigne GJ, Kato T, Kolta A, Sessle BJ: Neurobiological mechanisms involved in sleep bruxism. Crit Rev Oral Biol Med 2003;14:30–46.
37 Maixner W: Pain modulatory systems; in Lund JP, Lavigne GJ, Dubner R, Sessle BJ (eds): Orofacial Pain: From Basic Science to Clinical Management. Chicago, Quintessence, 2001, pp 79–91.
38 Chiang CY, Hu B, Park SJ, Zhang S, Kwan CL, Hu JW, Dostrovsky JO, Sessle BJ: Purinergic and NMDA-receptor mechanisms underlying tooth pulp stimulation-induced central sensitization in trigeminal nociceptive neurons; in Dostrovsky JO, Carr DB, Koltzenburg M (eds): Proceedings of the 10th World Congress on Pain: Progress in Pain Research and Management. Seattle, IASP Press, 2003, vol 24, pp 345–354.
39 Xie YF, Zhang S, Chiang CY, Hu JW, Dostrovsky JO, Sessle BJ: Involvement of glia in central sensitization in trigeminal subnucleus caudalis (medullary dorsal horn). Brain Behav Immun 2007; in press.

Barry J. Sessle
Professor and Canada Research Chair
Faculty of Dentistry, University of Toronto
124 Edward Street
Toronto, Ont. M5G 1G6 (Canada)
Tel. +1 416 979 4921, ext. 4336, Fax +1 416 979 4936
E-Mail barry.sessle@dentistry.utoronto.ca

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 75–90

Dental Pain

Pathophysiology and Management

Asma A. Khan, Kenneth M. Hargreaves

Department of Endodontics, University of Texas Health Science Center at San Antonio, San Antonio, Tex., USA

Abstract

Epidemiological studies indicate that odontalgia represents the most prevalent form of orofacial pain, with about 12–14% of the population reporting a history of odontalgia over a 6-month period. The accurate diagnosis and management of odontogenic pain requires a thorough knowledge of the mechanisms contributing to the activation and sensitization of pulpal and periradicular nociceptors. This chapter reviews the pathophysiology of pulpal and periradicular conditions which result in odontalgia and provides clinical guidelines for the diagnosis and management of dental pain.

Many patients report that the fear of dental pain represents a major barrier preventing their access to routine dental care [1, 2]. Thus, the effective diagnosis and treatment of dental pain represent major skills that provide not only symptomatic relief, but also foster the continued development and maintenance of oral health. Since odontogenic pain afflicts about 12–14% of the population [3] and is one of the most common forms of orofacial pain, this chapter focuses on mechanisms of odontogenic pain and therapeutic strategies for treating it.

As an organizational framework, we will divide our review of odontogenic pain into pulpal and periradicular pain mechanisms. However, the skilled clinician realizes that both can occur simultaneously in many patients.

Pulpal Pain

Pathophysiology

Pulpalgia is an important diagnostic feature of symptomatic pulpal inflammation. A number of pathological factors contribute to the induction and maintenance

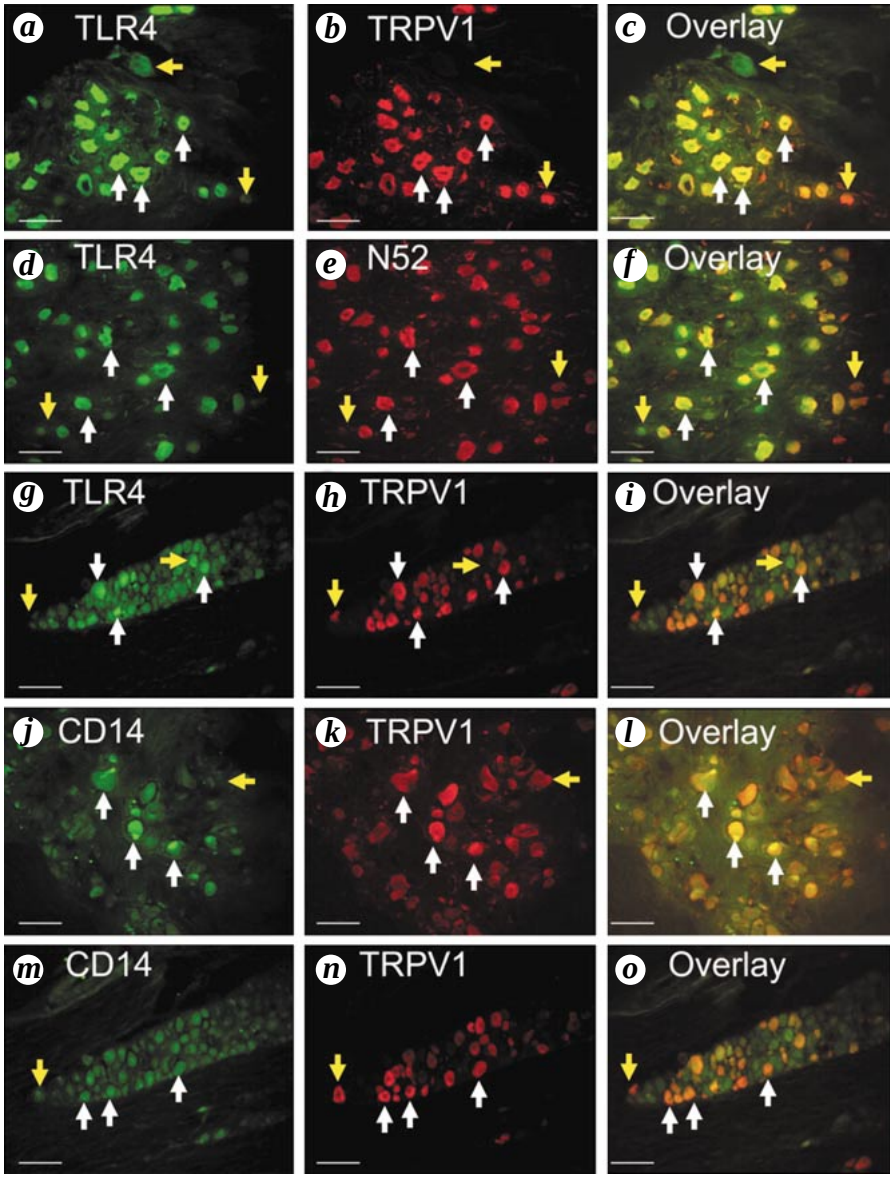

Fig. 1. Expression patterns of Toll-like receptor 4 (TLR4) and CD14 in trigeminal sensory neurons. White arrows depict examples of neurons expressing both markers for each row of 3 images, and gray arrows depict examples of neurons that express one but not both markers. Human trigeminal neurons were evaluated for colocalization of TLR4 (***a***, ***d***), CD14 (***j***), with a marker for the capsaicin-sensitive subclass of nociceptors (TRPV1, ***b***, ***c*** for TLR4 and ***k***, ***l*** for CD14), or a marker of myelinated sensory neurons (N52, ***e***, ***f***). Rat trigeminal

of inflammation of the dental pulp. These include bacterial invasion through carious lesions and crown fractures, and trauma due to restorative procedures [4–7]. Microorganisms are believed to be the most common etiological factor in the induction of pulpal inflammation [8–11]. Symptomatic teeth with carious exposures contain higher levels of endotoxins than asymptomatic caries teeth and caries-free teeth [5]. As shown in figure 1, a recent study has demonstrated that the capsaicin-sensitive subclass of trigeminal nociceptors express Toll-4 and CD14 receptors [12].

These data support the hypothesis that pulpal nociceptors can directly detect bacterial endotoxin, suggesting a direct mechanism for pain due to infection. Pulpal inflammation and necrosis can also result from certain restorative procedures including crown preparation and fabrication of temporary crowns [6, 13]; these responses could be due to iatrogenic injury or secondary to coronal microleakage.

Pulpal inflammation is mediated by a large number of endogenous factors including proinflammatory cytokines, neurotrophic factors, products of the arachidonic acid pathway, bradykinin and others. All of these factors are capable of activating and/or sensitizing peripheral nociceptors (pain-sensing neurons). Neurotrophic factors such as nerve growth factor (NGF) are produced by fibroblasts, mast cells and macrophages during inflammation. Pulpal inflammation results in an increase in the NGF content [13] which is known to sensitize or activate nociceptors [14, 15]. NGF also induces the release of proinflammatory cytokines such as interleukin 1 and tumor necrosis factor α [16]. These cytokines have been implicated in a number of inflammatory conditions including pulpitis [17, 18], periodontitis [19, 20] and arthritis [21, 22]. Both interleukin 1 and tumor necrosis factor α are known to modulate nociceptors and play an important role in central and peripheral sensitization [23–28].

Bradykinin is another potent mediator of both pain and inflammation. As seen in figure 2, bradykinin levels are elevated in pulps diagnosed as irreversibly inflamed as compared to those with a normal clinical diagnosis [29].

Other inflammatory mediators include products of the arachidonic acid pathway. The expression of the inducible isoform of cyclooxygenase, cyclooxygenase 2, is upregulated in inflamed pulps [30–32], which contributes to the production of proinflammatory prostaglandins (PG), such as PGE_2. Inflamed pulps contain higher levels of PGE_2 as compared to normal pulps [33], and this PG is known to sensitize nociceptors [34–37].

neurons were evaluated for colocalization of TLR4 with TRPV1 (***g–i***) and CD14 with TRPV1 (***m–o***). From Wadachi and Hargreaves [12], reproduced with permission from the International Association for Dental Research.

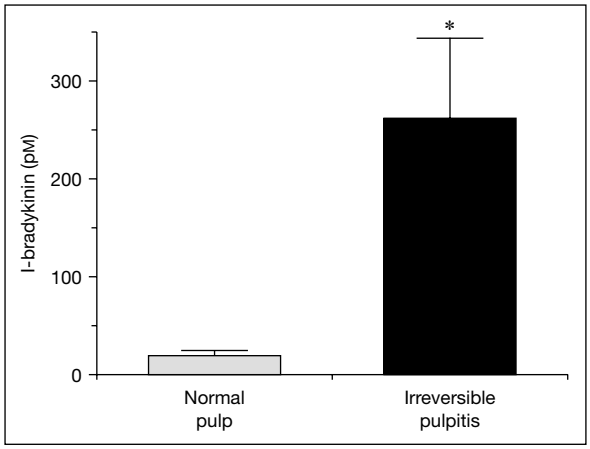

Fig. 2. Levels of bradykinin in human dental pulp with clinical diagnosis of normal or irreversible pulpitis. *$p < 0.05$. From Lepinski et al. [29], reproduced with permission from the American Academy of Endodontics.

All of the mediators mentioned above as well as others modulate the function of sensory nerve fibers present in the pulp. Most of the sensory neurons innervating the pulp have unmyelinated fibers with only approximately one eighth to one third being myelinated [38–41]. The myelinated afferent fibers in the pulp are thought to convey sharp pain impulses, while the unmyelinated fibers are thought to convey the perception of dull, aching or throbbing pain [42]. A subpopulation of the neurons innervating the pulp contain neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP), neuropeptide Y, neurokinin A and vasoactive intestinal peptide [43–45]. Activation of peptidergic neurons may result in the release of neuropeptides, which is associated with the development of neurogenic inflammation. Numerous studies have reported an increase in the content of neuropeptides in inflamed pulps as compared to normal pulps [46–48]. For example, experimentally induced lesions in rat molars resulted in the sprouting of nerve fibers into the inflamed pulp present adjacent to the lesion and was accompanied by an increase in the content of both CGRP and SP (fig. 3) [50].

This increase in CGRP and SP in inflamed pulps has also been reported in clinical studies [51–54]. As shown in figure 4, an 8-fold increase in SP was reported in pulps with a clinical diagnosis of irreversible pulpitis as compared to clinically normal pulps [53].

The excitability of neurons is dependent upon ion channels which are specialized membrane proteins that act to gate ion flux across the plasma

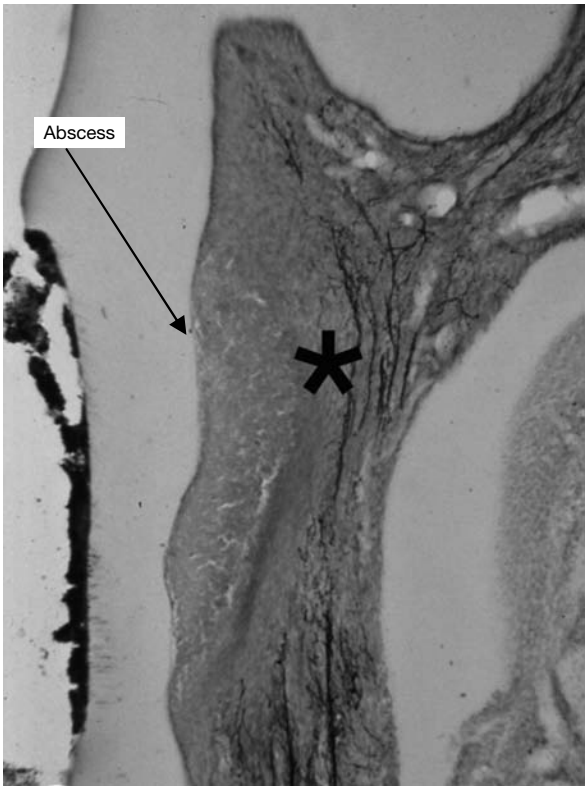

Fig. 3. Sprouting of immunoreactive CGRP fibers into the inflamed pulps of rat molars. The asterisk indicates the site of reparative dentin formation. Reproduced with permission from Taylor and Byers [49], reproduced with permission from Elsevier Science Ltd.

membrane, leading to either depolarization (i.e. 'excitation') or hyperpolarization (i.e. 'inhibition'). Nociceptors express various types of ion channels, including the tetrodotoxin-resistant voltage-gated sodium channel NaV 1.8 and members of the transient receptor potential (TRP) family. It is important to understand both the expression pattern of ion channels on nociceptors and the effects of drugs on their activity. For example, local anesthetics such as lidocaine act to block sodium channels, thereby reducing the ability of the terminal to depolarize and trigger a sustaining action potential back to the central nervous system. Similarly, opioids inhibit calcium channel activities, leading to reduced nerve function. The sodium channel NaV 1.8 (previously known as SNS1/PN3) is expressed on nociceptors and is upregulated in inflamed pulps (fig. 5) [55].

A number of mediators, including PGE_2, NGF and serotonin, rapidly and significantly increase the activity of NaV 1.8 [56, 57]. Importantly, the sensitivity

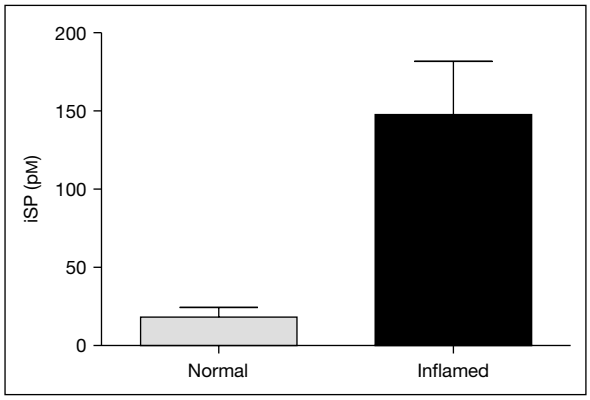

Fig. 4. Immunoreactive substance P (iSP) levels in human dental pulp with clinical diagnosis of normal or irreversible pulpitis. From Bowles et al. [53], reproduced with permission from the American Association of Endodontists.

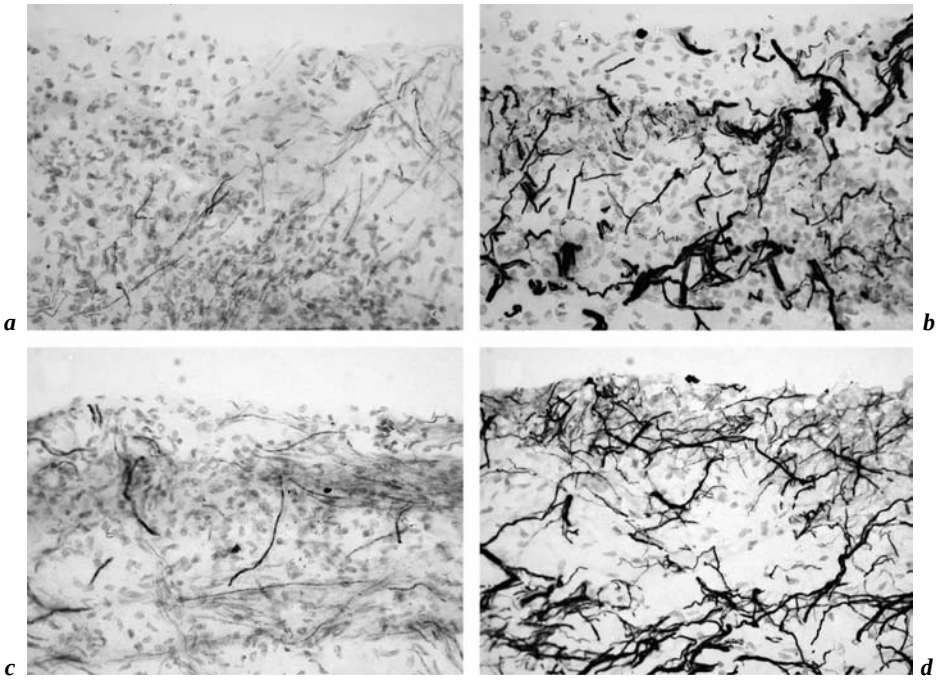

Fig. 5. Immunoreactive nerve fibers in painful (right column) and nonpainful (left column) human pulps. Staining with antibodies to NaV 1.8 (***a***, ***c***) and neurofilament (***b***, ***d***). From Renton et al. [55], reproduced with permission from Biomed Central.

Table 1. Comparison of the amount of local anesthetic in the dental cartridge to the concentration required to inhibit tetrodotoxin-resistant sodium channels

Anesthetic	IC_{50} TTX-R	Concentration in dental cartridge	Amount in dental cartridge
Lidocaine	326 mM	2% solution	227 times > IC_{50}
Bupivacaine	57 mM	0.5% solution	263 times > IC_{50}
Mepivacaine	166 mM	3% solution	639 times > IC_{50}

TTX-R = Tetrodotoxin-resistant. IC_{50} data from Brau and Elliott [59].

of NaV 1.8 to lidocaine is about one quarter of that of other sodium channels, and this is thought to account, in part, for the failure of local anesthetics in inflamed tissues [58]. Indeed, available local anesthetics differ in their IC_{50} concentration for inhibiting these channels. As shown in table 1, these differences in IC_{50}, coupled with known differences in the concentration of anesthetics in dental cartridges, allow one to determine which anesthetic formulation contains the greatest amount of drug required to block tetrodotoxin-resistant sodium channels.

The TRP ion channels transduce thermal, mechanical and chemical stimuli. They include TRP vanilloid type 1 (TRPV1) which is activated by noxious heat (≥43°C), protons, arachidonic acid metabolites, endocannabinoids and capsaicin. TRPV1 is believed to play a major role in peripheral sensitization, including the development of both allodynia (reduced pain thresholds) and hyperalgesia (increased responsiveness to painful stimuli). Peripheral sensitization could potentially reduce the activation threshold of TRPV1 from noxious temperatures (i.e. approx. 42°C) to close to body temperature. This phenomenon is thought to account for the clinical presentation of patients with irreversible pulpitis where the spontaneous pain is attenuated by application of cold. In these cases, it has been assumed that the spontaneous pain is due to thermal allodynia resulting in activation of nociceptors at innocuous temperatures (i.e. 37°C). While initial studies focused on the role of TRPV1 in peripheral sensitization, results from recent investigations suggest that other TRP channels may play an equal or more important role in the development of peripheral sensitization [60–62].

In addition to sensory neurons, the pulp is also innervated by sympathetic neurons which regulate pulpal blood flow. Activation of sympathetic fibers inhibits the exocytotic activity of peptidergic sensory neurons in the pulp [63]. It is likely that this constitutes one mechanism by which sympathetic fibers attenuate neurogenic inflammation.

Clinical Presentation

Inflamed pulps respond to thermal stimuli in an exaggerated manner. Pulpal inflammation is classified into reversible pulpitis and irreversible pulpitis.

Patients with reversible pulpitis usually present with a chief complaint of sharp pain elicited by thermal stimuli. These pulps respond to cold or heat in an exaggerated but brief manner.

On the other hand, teeth with irreversible pulpitis often respond to cold or heat and lead to an exaggerated pain report and lingering pain; pain may also be spontaneous in some cases. The clinical presentation of irreversible pulpitis is varied. This is likely due to variations in peripheral and central sensitization of the nociceptive system. In general, spontaneous pain may be due to allodynia where normal innocuous stimuli elicit pain (e.g. thermal allodynia where 37°C activates nociceptors or mechanical allodynia where systolic increases in blood pressure activate nociceptors in a periodic or 'throbbing' fashion). Similarly, the exaggerated pain report following pulp stimulation is a clinical example of hyperalgesia. Some patients present with severe spontaneous pain relieved by cold, while others report that application of cold and/or heat elicits severe pain which lasts for several seconds to minutes.

Management

The management of pain associated with reversible pulpitis is to identify and remove the etiology and to maintain the vitality of the pulp. Conversely, the management of pain associated with irreversible pulpitis generally involves the initiation of nonsurgical endodontic therapy. In one interesting clinical trial, patients diagnosed as having irreversible pulpitis received an intraosseous injection of either a steroid or a placebo [64]. Although the teeth had the diagnosis of 'irreversible' pulpitis, the steroid injection significantly reduced pain without pulpal necrosis evident at a 1-week follow-up. This intriguing finding suggests that, at least in certain cases, a steroid injection might reverse 'irreversible' pulpitis. However, prior to any clinical recommendation, further studies with long-term follow-up are required. As local anesthetics are much less effective in inflamed tissues as compared to normal tissues [65], obtaining adequate local anesthesia may be challenging in teeth with irreversible pulpitis. The failure of local anesthetic injections in patients with irreversible pulpitis is 8 times higher than in normal control patients [66]. In a clinical trial of patients with pulpitis ($n = 25$) of one of their mandibular teeth, inferior alveolar nerve block (2% lidocaine with 1:100,000 epinephrine) resulted in 100% incidence of lip numbness, but only 38% of pulpal anesthesia (fig. 6) [67]. Thus, a positive lip sign does not necessarily indicate adequate pulpal anesthesia in teeth with inflamed pulps.

Several therapeutic approaches can be used to enhance the efficacy of local anesthetics in patients with inflamed pulps. One of these is the use of a fast-acting

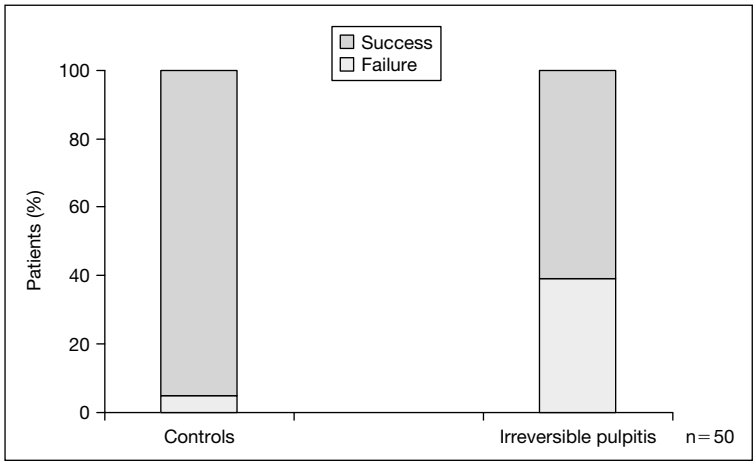

Fig. 6. Prevalence of failure to obtain adequate local anesthesia in teeth with a clinical diagnosis of normal pulp or irreversible pulpitis: failure is 8-fold higher in patients with irreversible pulpitis. From Hargreaves et al. [67], copyright retained by author.

anti-inflammatory agent, such as a nonsteroidal anti-inflammatory drug or a steroid. These substances inhibit the synthesis of PGE_2, resulting in the attenuation of pulpal nociceptor sensitization. As mentioned earlier, PGE_2 stimulates the activity of the sodium channel NaV 1.8 which is relatively resistant to lidocaine. A number of clinical trials have evaluated the analgesic effect of the injectable nonsteroidal anti-inflammatory drug ketorolac tromethamine in endodontic as well as orthodontic and ophthalmic procedures. While the majority of these investigations [68–71] as well as a systematic review [72] have concluded that ketorolac tromethamine produces significant analgesia when injected locally, a recent study has reported that it has limited analgesic efficacy [73].

Another approach to obtain effective local anesthesia is to use an anesthetic with a lower pKa such as 3% mepivacaine. This decreases the potential for ion trapping and thus increases the concentration of local anesthetic molecules in the base form required for diffusion across the nerve membrane. Increasing the dose of local anesthetic used is yet another way to obtain adequate pulpal anesthesia. Using a larger dose of the local anesthetic would expose a greater length of the nerve to the anesthetic agent used and thus increase the likelihood of conduction blockade [74]. In case of pulpitis involving a mandibular tooth, an effective strategy is to deliver one cartridge of the local anesthetic in the conventional location for inferior alveolar nerve block, followed by administration of a second cartridge higher in the pterygomandibular space. This not only increases the length of the nerve exposed to the local

anesthetic, but also blocks the myelohyoid nerve before it branches off the inferior alveolar nerve [75].

Intraligamentary and intraosseous techniques can also be used to obtain adequate pulpal anesthesia. Several clinical trials have demonstrated that intraosseous injections significantly enhance pulpal anesthesia after inferior alveolar nerve blocks in patients with irreversible pulpitis [76–78]. If the use of intraligamentary and intraosseous techniques does not result in adequate anesthesia, intrapulpal injection may be used as a final option [79, 80].

While it has been well established that the best way to manage irreversible pulpitis is by providing endodontic therapy, a recent study has reported that 16.8% of endodontists prescribe antibiotics to patients with irreversible pulpitis [81]. A double-blind, randomized, placebo-controlled clinical trial demonstrated that administration of penicillin had no effect on the pain, percussion sensitivity and the number of analgesic medications taken by patients with irreversible pulpitis [82]. Thus, the use of antibiotics in the management of irreversible pulpitis is unnecessary and could potentially contribute to the development of antibiotic-resistant bacterial strains.

Periradicular Pain

Pathophysiology

Pain associated with the periradicular tissues is an essential feature of acute periradicular inflammatory conditions (e.g. acute exacerbation of chronic periradicular periodontitis, acute periradicular periodontitis, acute apical abscess). Periradicular pain may be associated with a pulpal pathology, such as an irreversibly inflamed pulp, a necrotic pulp or failing endodontic treatment. A recent study of 198 patients reported that 57.2% of teeth with irreversible pulpitis also had apical periodontitis [83]. Periradicular pain is not always associated with a pulpal pathology and may also result from occlusal trauma.

The underlying mechanisms leading to sensitization and/or activation of periradicular nociceptors are essentially the same as those involved in pulpal pain. Periradicular pain in teeth with infected pulps represents an inflammatory and immune response to microorganisms and their products. Several studies have examined the levels of inflammatory mediators in periapical tissues and have attempted to correlate the levels of these mediators with clinical signs and symptoms [84–87]. Most of these investigations are inconclusive due to small sample sizes. A recent study reported that periapical exudates collected from teeth with large periradicular radiolucencies contain higher levels of PGE_2 than those collected from teeth with smaller radiolucent lesions [84].

One characteristic feature of chronic apical periodontitis is extensive sprouting of peripheral peptidergic nerve fibers into the periradicular tissue. This extensive neuronal arborization occurs during the onset of periapical lesions with a selective increase in the neuropeptides CGRP and SP [48, 50, 88]. It has been suggested that this sprouting is due, at least in part, to increased expression of NGF in the inflamed tissue [40].

Interestingly, a recent clinical study reported that patients with a certain polymorphism of the interleukin 1β gene have a 7-fold increased risk of developing persistent apical periodontitis after technically satisfactory nonsurgical root canal treatment [89], suggesting that genetic host factors modulate the periradicular response to endodontic treatment. However, it is not yet known whether this or other polymorphisms alter the risk for developing odontogenic pain. This is clearly an important area of future research.

Clinical Presentation

Periradicular pain may manifest as spontaneous pain or pain on biting. The latter is due to mechanical allodynia, which is defined by reduced mechanical pain thresholds. Mechanical allodynia shows a high sensitivity for detecting periradicular pain as compared to pulpal pain (odds ratio of 6.9 vs. pulpitis; $p < 0.01$) [90]. The most common clinical method for measuring mechanical allodynia in a tooth is a percussion test, often conducted using a mirror handle [91]. To establish a baseline for comparison, the test is also conducted on adjacent normal teeth. In fractured teeth, percussing on the tooth with a mirror handle may not always replicate the patient's chief complaint of pain on biting. In such teeth, pressure must be applied to individual cusps or teeth in order to replicate the chief complaint.

Management

The management of periradicular pain involves identifying and removing the causative factors. If the pain is due to occlusal trauma, treatment may just involve adjusting the occlusion. However, if the root canal space is infected, endodontic therapy must be initiated. Obtaining adequate local anesthesia in teeth with periradicular periodontitis is not as challenging as in teeth with irreversible pulpitis. Chemomechanical debridement of the root canal space reduces the microorganisms present and results in attenuation of the periradicular pain. This reduction in symptoms takes a few days, and it may be advisable to place the patient on analgesics for 3–4 days. Another effective strategy is to reduce the occlusal surface of the tooth so that it no longer contacts the opposing teeth. In teeth with acute apical abscesses, it is important to establish a pathway for drainage. This involves performing incision and drainage or trephination. A systematic review on the management of localized acute apical abscesses in

Table 2. Antibiotics and pain control [92]

Meta-analysis of antibiotics for AAA
• Found 35 relevant studies; 8 were RCTs
• Absence of infection: OR = NS
• Absence of pain: OR = NS
• Absence of pain and infection: OR = NS
• Recommended: drain abscess via pulpectomy and/or IND; antibiotics no additional benefit for AAA
• Recommended: RX antibiotics when patients have systemic complications (fever, lymphadenopathy, cellulitis)

AAA = Acute apical abscess; IND = incision for drainage; NS = not significant; OR = odds ratio; RCTs = randomized controlled trials; RX = prescribe.

the permanent dentition concluded that drainage results in significant pain relief and that antibiotics are of no additional benefit (table 2) [92]. This review suggested that antibiotics should only be prescribed to patients who are immunocompromised or to those who have signs of systemic involvement.

Future Directions

Recent studies indicate that opioids have an antinociceptive effect when administered into inflamed tissues. These effects are not seen when opioids are injected into normal tissues. Proinflammatory agents like bradykinin trigger the development of competence of opioid receptors [93]. A series of double-blind clinical trials using the oral surgery model and the endodontic model of hyperalgesia elegantly demonstrated the presence of peripheral opioid analgesia [94].

A recent investigation indicated that red-haired women are more resistant to the effects of subcutaneous lidocaine than dark-haired women, particularly in response to stimuli known to activate Aδ fibers [95]. Additional studies are needed to replicate these findings in odontogenic pain patients and to elucidate whether redheads simply require higher dosages of lidocaine to obtain adequate anesthesia.

References

1 Dionne RA, Gordon SM, McCullagh LM, Phero JC: Assessing the need for anesthesia and sedation in the general population. J Am Dent Assoc 1998;129:167–173.
2 Gatchel RJ, Ingersoll BD, Bowman L, Robertson MC, Walker C: The prevalence of dental fear and avoidance: a recent survey study. J Am Dent Assoc 1983;107:609–610.

3 Lipton JA, Ship JA, Larach-Robinson D: Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 1993;124:115–121.
4 Lynch CD, McConnell RJ: The cracked tooth syndrome. J Can Dent Assoc 2002;68:470–475.
5 Khabbaz MG, Anastasiadis PL, Sykaras SN: Determination of endotoxins in the vital pulp of human carious teeth: association with pulpal pain. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:587–593.
6 Mjör IA, Odont D: Pulp-dentin biology in restorative dentistry. 2. Initial reactions to preparation of teeth for restorative procedures. Quintessence Int 2001;32:537–551.
7 Zöllner A, Gaengler P: Pulp reactions to different preparation techniques on teeth exhibiting periodontal disease. J Oral Rehabil 2000;27:93–102.
8 Camps J, Dejou J, Remusat M, About I: Factors influencing pulpal response to cavity restorations. Dent Mater 2000;16:432–440.
9 Kakehashi S, Stanley HR, Fitzgerald RJ: The effects of surgical exposures of dental pulps in germfree and conventional laboratory rats. Oral Surg Oral Med Oral Pathol 1965;20:340–349.
10 Martin FE: Carious pulpitis: microbiological and histopathological considerations. Aust Endod J 2003;29:134–137.
11 Reeves R, Stanley HR: The relationship of bacterial penetration and pulpal pathosis in carious teeth. Oral Surg Oral Med Oral Pathol 1966;22:59–65.
12 Wadachi R, Hargreaves KM: Trigeminal nociceptors express TLR-4 and CD14: a mechanism for pain due to infection. J Dent Res 2006;85:49–53.
13 Byers MR, Swift ML, Wheeler EF: Reactions of sensory nerves to dental restorative procedures. Proc Finn Dent Soc 1992;88(suppl 1):73–82.
14 McMahon SB: NGF as a mediator of inflammatory pain. Philos Trans R Soc Lond B Biol Sci 1996;351:431–440.
15 Woolf CJ: Phenotypic modification of primary sensory neurons: the role of nerve growth factor in the production of persistent pain. Philos Trans R Soc Lond B Biol Sci 1996;351:441–448.
16 Bonini S, Rasi G, Bracci-Laudiero ML, Procoli A, Aloe L: Nerve growth factor: neurotrophin or cytokine? Int Arch Allergy Immunol 2003;131:80–84.
17 Tani-Ishii N, Wang CY, Stashenko P: Immunolocalization of bone-resorptive cytokines in rat pulp and periapical lesions following surgical pulp exposure. Oral Microbiol Immunol 1995;10: 213–219.
18 Pezelj-Ribaric S, Anic I, Brekalo I, Miletic I, Hasan M, Simunovic-Soskic M: Detection of tumor necrosis factor alpha in normal and inflamed human dental pulps. Arch Med Res 2002;33: 482–484.
19 Bascones A, Gamonal J, Gomez M, Silva A, Gonzalez MA: New knowledge of the pathogenesis of periodontal disease. Quintessence Int 2004;35:706–716.
20 Kornman KS: Interleukin 1 genetics, inflammatory mechanisms, and nutrigenetic opportunities to modulate diseases of aging. Am J Clin Nutr 2006;83:475S–483S.
21 Hsu HC, Wu Y, Mountz JD: Tumor necrosis factor ligand-receptor superfamily and arthritis. Curr Dir Autoimmun 2006;9:37–54.
22 Schett G, Smolen JS: New insights in the mechanism of bone loss in arthritis. Curr Pharm Des 2005;11:3039–3049.
23 Sachs D, Cunha FQ, Poole S, Ferreira SH: Tumour necrosis factor-α, interleukin-1β and interleukin-8 induce persistent mechanical nociceptor hypersensitivity. Pain 2002;96:89–97.
24 Cunha FQ, Poole S, Lorenzetti BB, Ferreira SH: The pivotal role of tumour necrosis factor αin the development of inflammatory hyperalgesia. Br J Pharmacol 1992;107:660–664.
25 Cunha JM, Cunha FQ, Poole S, Ferreira SH: Cytokine-mediated inflammatory hyperalgesia limited by interleukin-1 receptor antagonist. Br J Pharmacol 2000;130:1418–1424.
26 Sommer C, Kress M: Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci Lett 2004;361:184–187.
27 Cunha TM, Verri WA Jr, Silva JS, Poole S, Cunha FQ, Ferreira SH: A cascade of cytokines mediates mechanical inflammatory hypernociception in mice. Proc Natl Acad Sci USA 2005;102:1755–1760.
28 Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bonventre JV, Woolf CJ: Interleukin-1β-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410:471–475.

29 Lepinski AM, Hargreaves KM, Goodis HE, Bowles WR: Bradykinin levels in dental pulp by microdialysis. J Endod 2000;26:744–747.
30 Nakanishi T, Shimizu H, Hosokawa Y, Matsuo T: An immunohistological study on cyclooxygenase-2 in human dental pulp. J Endod 2001;27:385–388.
31 Chang YC, Huang FM, Yang SF, Liu CM, Lai CC, Chan Y, Hsieh YS: Induction of cyclooxygenase-2 mRNA and protein expression in human pulp cells stimulated with black-pigmented bacteroides. J Endod 2003;29:240–243.
32 Chang YC, Yang SF, Huang FM, Liu CM, Tai KW, Hsieh YS: Proinflammatory cytokines induce cyclooxygenase-2 mRNA and protein expression in human pulp cell cultures. J Endod 2003;29: 201–204.
33 Miyauchi M, Takata T, Ito H, Ogawa I, Kobayashi J, Nikai H, Ijuhin N: Immunohistochemical demonstration of prostaglandins E_2, $F_{2\alpha}$, and 6-keto-prostaglandin $F_{1\alpha}$ in rat dental pulp with experimentally induced inflammation. J Endod 1996;22:600–602.
34 Lopshire JC, Nicol GD: Activation and recovery of the PGE_2-mediated sensitization of the capsaicin response in rat sensory neurons. J Neurophysiol 1997;78:3154–3164.
35 Goodis HE, Bowles WR, Hargreaves KM: Prostaglandin E_2 enhances bradykinin-evoked iCGRP release in bovine dental pulp. J Dent Res 2000;79:1604–1607.
36 Gold MS, Reichling DB, Shuster MJ, Levine JD: Hyperalgesic agents increase a tetrodotoxin-resistant Na^+ current in nociceptors. Proc Natl Acad Sci USA 1996;93:1108–1112.
37 Evans AR, Vasko MR, Nicol GD: The cAMP transduction cascade mediates the PGE_2-induced inhibition of potassium currents in rat sensory neurones. J Physiol 1999;516:163–178.
38 Byers MR: Dynamic plasticity of dental sensory nerve structure and cytochemistry. Arch Oral Biol 1994;39(suppl):13S–21S.
39 Johnson DC: Innervation of teeth: qualitative, quantitative, and developmental assessment. J Dent Res 1985;64:555–563.
40 Byers MR, Narhi MV: Dental injury models: experimental tools for understanding neuroinflammatory interactions and polymodal nociceptor functions. Crit Rev Oral Biol Med 1999;10:4–39.
41 Trowbridge HO: Review of dental pain – Histology and physiology. J Endod 1986;12:445–452.
42 Narhi M, Jyvasjarvi E, Virtanen A, Huopaniemi T, Ngassapa D, Hirvonen T: Role of intradental A- and C-type nerve fibres in dental pain mechanisms. Proc Finn Dent Soc 1992;88(suppl 1): 507–516.
43 Heyeraas KJ, Kvinnsland I, Byers MR, Jacobsen EB: Nerve fibers immunoreactive to protein gene product 9.5, calcitonin gene-related peptide, substance P, and neuropeptide Y in the dental pulp, periodontal ligament, and gingiva in cats. Acta Odontol Scand 1993;51:207–221.
44 Awawdeh LA, Lundy FT, Linden GJ, Shaw C, Kennedy JG, Lamey PJ: Quantitative analysis of substance P, neurokinin A and calcitonin gene-related peptide in gingival crevicular fluid associated with painful human teeth. Eur J Oral Sci 2002;110:185–191.
45 Casasco A, Calligaro A, Casasco M, Springall DR, Polak JM, Poggi P, Marchetti C: Peptidergic nerves in human dental pulp: an immunocytochemical study. Histochemistry 1990;95:115–121.
46 Buck S, Reese K, Hargreaves KM: Pulpal exposure alters neuropeptide levels in inflamed dental pulp and trigeminal ganglia: evaluation of axonal transport. J Endod 1999;25:718–721.
47 Grutzner EH, Garry MG, Hargreaves KM: Effect of injury on pulpal levels of immunoreactive substance P and immunoreactive calcitonin gene-related peptide. J Endod 1992;18:553–557.
48 Kimberly CL, Byers MR: Inflammation of rat molar pulp and periodontium causes increased calcitonin gene-related peptide and axonal sprouting. Anat Rec 1988;222:289–300.
49 Taylor PE, Byers MR: An immunocytochemical study of the morphological reaction of nerves containing calcitonin gene-related peptide to microabscess formation and healing in rat molars. Arch Oral Biol 1990;35:629–638.
50 Byers MR, Taylor PE, Khayat BG, Kimberly CL: Effects of injury and inflammation on pulpal and periapical nerves. J Endod 1990;16:78–84.
51 Awawdeh L, Lundy FT, Shaw C, Lamey PJ, Linden GJ, Kennedy JG: Quantitative analysis of substance P, neurokinin A and calcitonin gene-related peptide in pulp tissue from painful and healthy human teeth. Int Endod J 2002;35:30–36.
52 Rodd HD, Boissonade FM: Substance P expression in human tooth pulp in relation to caries and pain experience. Eur J Oral Sci 2000;108:467–474.

53 Bowles WR, Withrow JC, Lepinski AM, Hargreaves KM: Tissue levels of immunoreactive substance P are increased in patients with irreversible pulpitis. J Endod 2003;29:265–267.
54 Caviedes-Bucheli J, Correa-Ortiz JA, García LV, López-Torres R, Lombana N, Muñoz HR: The effect of cavity preparation on substance P expression in human dental pulp. J Endod 2005;31: 857–859.
55 Renton T, Yiangou Y, Plumpton C, Tate S, Bountra C, Anand P: Sodium channel Nav1.8 immunoreactivity in painful human dental pulp. BMC Oral Health 2005;5:5.
56 Gold MS, Zhang L, Wrigley DL, Traub RJ: Prostaglandin E_2 modulates TTX-R I_{Na} in rat colonic sensory neurons. J Neurophysiol 2002;88:1512–1522.
57 Rush AM, Waxman SG: PGE_2 increases the tetrodotoxin-resistant Nav1.9 sodium current in mouse DRG neurons via G-proteins. Brain Res 2004;1023:264–271.
58 Roy ML, Narahashi T: Differential properties of tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels in rat dorsal root ganglion neurons. J Neurosci 1992;12:2104–2111.
59 Brau ME, Elliott JR: Local anaesthetic effects on tetrodotoxin-resistant Na^+ currents in rat dorsal root ganglion neurons. Eur J Anaesthesiol 1998;15:80–88.
60 Obata K, Katsura H, Mizushima T, Yamanaka H, Kobayashi K, Dai Y, Fukuoka T, Tokunaga A, Tominaga M, Noguchi K: TRPA1 induced in sensory neurons contributes to cold hyperalgesia after inflammation and nerve injury. J Clin Invest 2005;115:2393–2401.
61 Numazaki M, Tominaga M: Nociception and TRP channels. Curr Drug Targets CNS Neurol Disord 2004;3:479–485.
62 Inoue R, Hanano T, Shi J, Mori Y, Ito Y: Transient receptor potential protein as a novel non-voltage-gated Ca^{2+} entry channel involved in diverse pathophysiological functions. J Pharmacol Sci 2003;91:271–276.
63 Hargreaves KM, Bowles WR, Jackson DL: Intrinsic regulation of CGRP release by dental pulp sympathetic fibers. J Dent Res 2003;82:398–401.
64 Gallatin E, Reader A, Nist R, Beck M: Pain reduction in untreated irreversible pulpitis using an intraosseous injection of Depo-Medrol. J Endod 2000;26:633–638.
65 Walton RE, Torabinejad M: Managing local anesthesia problems in the endodontic patient. J Am Dent Assoc 1992;123:97–102.
66 Hargreaves KM: Neurochemical factors in injury and inflammation in orofacial tissues; in Lavigne G, Lund J, Sessle B, Dubner R (eds): Orofacial Pain: Basic Sciences to Clinical Management. Chicago, Quintessence, pp 59–66.
67 Hargreaves KM, Dryden J, Schwarze M, Garcia N, Martin WJ, Flores CM: Development of a model to evaluate phenotypic plasticity in human nociceptors. Abstr Soc Neurosci 2001;27:83.
68 Curtis P Jr, Gartman LA, Green DB: Utilization of ketorolac tromethamine for control of severe odontogenic pain. J Endod 1994;20:457–459.
69 Penniston SG, Hargreaves KM: Evaluation of periapical injection of ketorolac for management of endodontic pain. J Endod 1996;22:55–59.
70 Brint SF, Cheetham JK, De Gryse R, Abel ML, Thompson VM, Rosenthal A: Efficacy and safety of nonpreserved ketorolac ophthalmic solution in postoperative ocular pain following radial keratotomy. J Cataract Refract Surg 1999;25:41–49.
71 Rogers MJ, Johnson BR, Remeikis NA, BeGole EA: Comparison of effect of intracanal use of ketorolac tromethamine and dexamethasone with oral ibuprofen on post treatment endodontic pain. J Endod 1999;25:381–384.
72 Smith LA, Carroll D, Edwards JE, Moore RA, McQuay HJ: Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis. Br J Anaesth 2000;84:48–58.
73 Mellor AC, Dorman ML, Girdler NM: The use of an intra-oral injection of ketorolac in the treatment of irreversible pulpitis. Int Endod J 2005;38:789–792, discussion 792–784.
74 Franz DN, Perry RS: Mechanisms for differential block among single myelinated and non-myelinated axons by procaine. J Physiol 1974;236:193–210.
75 Wilson S, Johns P, Fuller PM: The inferior alveolar and myelohyoid nerves: an anatomic study and relationship to local anesthesia of the anterior mandibular teeth. J Am Dent Assoc 1984;108: 350–352.
76 Nusstein J, Kennedy S, Reader A, Beck M, Weaver J: Anesthetic efficacy of the supplemental X-tip intraosseous injection in patients with irreversible pulpitis. J Endod 2003;29:724–728.

77 Nusstein J, Reader A, Nist R, Beck M, Meyers WJ: Anesthetic efficacy of the supplemental intraosseous injection of 2% lidocaine with 1:100,000 epinephrine in irreversible pulpitis. J Endod 1998;24:487–491.
78 Reisman D, Reader A, Nist R, Beck M, Weaver J: Anesthetic efficacy of the supplemental intraosseous injection of 3% mepivacaine in irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;84:676–682.
79 Smith GN, Smith SA: Intrapulpal injection: distribution of an injected solution. J Endod 1983;9:167–170.
80 Van Gheluwe J, Walton R: Intrapulpal injection: factors related to effectiveness. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:38–40.
81 Yingling NM, Byrne BE, Hartwell GR: Antibiotic use by members of the American Association of Endodontists in the year 2000: report of a national survey. J Endod 2002;28:396–404.
82 Nagle D, Reader A, Beck M, Weaver J: Effect of systemic penicillin on pain in untreated irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:636–640.
83 Owatz CB, Khan AA, McCreary BF, Schindler WG, Schwartz SA, Keiser K, Hargreaves KM: Incidence and pain intensity in patients with irreversible pulpitis and acute periradicular periodontitis. J Endod 2006;32:233.
84 Alptekin NO, Ari H, Ataoglu T, Haliloglu S, Alptekin T, Serpek B: Neutrophil elastase levels in periapical exudates of symptomatic and asymptomatic teeth. J Endod 2005;31:350–353.
85 Takeichi O, Saito I, Tsurumachi T, Moro I, Saito T: Expression of inflammatory cytokine genes in vivo by human alveolar bone-derived polymorphonuclear leukocytes isolated from chronically inflamed sites of bone resorption. Calcif Tissue Int 1996;58:244–248.
86 Shimauchi H, Miki Y, Takayama S, Imai T, Okada H: Development of a quantitative sampling method for periapical exudates from human root canals. J Endod 1996;22:612–615.
87 Matsuo T, Ebisu S, Nakanishi T, Yonemura K, Harada Y, Okada H: Interleukin-1α and interleukin-1β periapical exudates of infected root canals: correlations with the clinical findings of the involved teeth. J Endod 1994;20:432–435.
88 Khayat BG, Byers MR, Taylor PE, Mecifi K, Kimberly CL: Responses of nerve fibers to pulpal inflammation and periapical lesions in rat molars demonstrated by calcitonin gene-related peptide immunocytochemistry. J Endod 1988;14:577–587.
89 Morsani JM, Mickel AK, Chogle S, Jones J, Han YW, Demko C, Ikegami A: Genetic predisposition to persistent apical periodontitis. J Endod 2006;32:233.
90 Klausen B, Helbo M, Dabelsteen E: A differential diagnostic approach to the symptomatology of acute dental pain. Oral Surg Oral Med Oral Pathol 1985;59:297–301.
91 Cohen SLF: Diagnostic Procedures, ed 9. St Louis, Mosby, 2006.
92 Matthews DC, Sutherland S, Basrani B: Emergency management of acute apical abscesses in the permanent dentition: a systematic review of the literature. J Can Dent Assoc 2003;69:660.
93 Patwardhan AM, Berg KA, Akopain AN, Jeske NA, Gamper N, Clarke WP, Hargreaves KM: Bradykinin induced functional competence and trafficking of the delta-opioid receptor in trigeminal nociceptors. Journal of Neuroscience 2005;25:8825–8832.
94 Dionne RA, Lepinski AM, Gordon SM, Jaber L, Brahim JS, Hargreaves KM: Analgesic effects of peripherally administered opioids in clinical models of acute and chronic inflammation. Clin Pharmacol Ther 2001;70:66–73.
95 Liem EB, Joiner TV, Tsueda K, Sessler DI: Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. Anesthesiology 2005;102:509–514.

Kenneth M. Hargreaves, DDS, PhD
Professor
Department of Endodontics
University of Texas Health Science Center at San Antonio
San Antonio, TX 78284 (USA)
Tel. +1 210 567 3388, Fax +1 210 567 3389, E-Mail hargreaves@uthscsa.edu

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 91–123

Myofascial Temporomandibular Disorder Pain

Pathophysiology and Management

Hans Jürgen Schindler[a], *Peter Svensson*[b]

[a]Karlsruhe, Germany; [b]Aarhus, Denmark

Abstract

Myofascial temporomandibular disorder (TMD) pain can be regarded as a regional manifestation of musculoskeletal disorders similar to those observed in other body regions. The painful local muscle disturbances are assumed to be associated with a variety of biophysiological risk factors. Therefore, myofascial TMD pain should be interpreted as a phenomenon determined and influenced by a multitude of factors which will have important implications for the management of these problems. Most myofascial TMDs are rather episodic (intermittent) in nature. In a considerable number of patients, however, the pain persists over a long period of time, despite therapeutic interventions. Structural changes in peripheral and central nervous nociceptive pathways may provide a neurobiological explanation for these refractory types of myofascial TMD pain. Since complex biopsychosocial interactions determine the development of these dysfunctional pain conditions, diagnostic instruments that consider somatic and psychological factors are needed to appropriately evaluate the patients' therapeutic needs. Results of an extensive literature search show that for the majority of patients, pain reduction or pain relief can be achieved with noninvasive reversible methods. Longitudinal short- and long-term studies have revealed that different therapeutic measures are similarly effective. In patients with persistent myofascial TMD of the jaw muscles associated with psychosocial impairment, additional involvement of a psychotherapist is crucial.

Pain in the jaw musculature is the most commonly reported pain of nondental origin in the orofacial region. Together with arthralgia of the temporomandibular joints, it is collectively referred to as 'temporomandibular disorder' (TMD) [1]. Muscle pain is difficult to localize. It is often characterized by dull pressure or a pulling sensation [2]. The pain is usually of mild to moderate intensity, and it is perceived as more intense when the muscles are strained (e.g. muscle palpation or

isometric contraction) as well as during jaw movements (e.g. chewing). The pain may be accompanied by limitations of mandibular movements and by perceived changes in tooth contacts related to altered sensorimotor function (caused by pain-adapted motor function). The muscle pain may be referred to and perceived in other areas, such as teeth or tooth groups, temporomandibular joints, middle ear, temples and eyes [3]. In these cases, the localization of the pain is different from the pain source, which has bearings on the differential diagnosis. Current recommendations for management include noninvasive approaches, including physical, pharmacological and psychological procedures.

Classification

Painful TMDs can be regarded as regional manifestations of musculoskeletal disorders similarly to those observed in other parts of the body (i.e. bone, muscles, joints and associated tissues).

The term 'myofascial pain', as used in the following, describes a number of painful muscle disturbances which are characterized by the patients' report of pain, tenderness and localized pressure pain on palpation. This stands in contrast to the interpretation of other authors [4], who associate myofascial pain exclusively with a specific pathophysiological entity, the so-called trigger points. However, in the present text, the term 'myofascial TMD pain' is preferred as a purely descriptive term without any reference to a particular pathophysiological mechanism.

Myofascial TMD pains are assumed to be associated with a variety of biomedical risk factors, such as hormonal, neuroendocrine and genetic dispositions, and biomechanical strain (see below), but currently the classification only relies on the symptomatology and not on underlying mechanisms or known etiological factors.

Most myofascial TMD pains can be easily managed, and they are rather episodic in nature [5], i.e. there can be periods with exacerbation of pain followed by remission which could be termed an 'intermittent' type of myofascial TMD pain. Nevertheless, an appreciable number of patients may suffer from 'persistent pain', i.e. from pain that lasts longer than expected in an acute pain condition (e.g. longer than 1, 2 or 3 weeks, depending on the severity of the tissue damage). As recently demonstrated [6], the prognosis of these patients can be made by psychometric evaluation (axis II of the Research Diagnostic Criteria for Temporomandibular Disorders or RDC/TMD [7]). This makes them distinguishable from the considerable number of TMD pain patients, where the pain continues over a long period of time despite therapeutic interventions. In these situations, additional pains are often simultaneously present in other areas

of the body [8]; however, these 'extratrigeminal' pain locations are seldom reported by patients to the dentists [9]. Myofascial TMD pain that lasts for a long period of time may lead to substantial psychosocial distress and associated psychological and behavioral reactions (e.g. impairment in the performance of daily tasks, restriction of social contacts, depressive preoccupation and other disturbances of emotional well-being) [10]. In the following, pain associated with 'psychosocial dysfunctions' will be considered as 'dysfunctional' pain [11], which is also included in current considerations of pain mechanisms [12].

In secondary and tertiary care TMD units (pain specialists or pain clinics), between 4.2% [13] and 46% [14] of the TMD population are dysfunctional pain patients. Conversely, in primary care settings (dental offices, nonspecialized clinics), the prevalence of those patients can be assumed to be between 5 and 10%.

Epidemiology

The majority of TMD patients suffer from myofascial pain or a combination of myofascial and temporomandibular joint pain [15–17]. Women, especially those in the fourth decade of their life (i.e. between 30 and 39 years), are up to 4 times more frequently affected than males [18]. The prevalence in children is slightly lower and the symptoms are usually much milder than in adults [18, 19]. The prevalence increases, however, with pubertal onset [20]. The prevalence of TMD pain in adults has been estimated to range between 2 and 18% for women and 0 and 10% for males [21, 22]. With regard to the differences of reported percentages, it has to be noted that epidemiological findings will obviously depend on classification – some investigations only look at palpation findings, others on patient reports. However, only about 3% of the TMD pain population demands active treatment [23]. Relatively few studies have examined the incidence of myofascial TMD pain (new cases per year) with a rigorous case definition, but there appear to be between 1.6 and 3.9% per year with about a tenth being 'dysfunctional' [24].

Pathophysiology

In the following paragraphs, the pathophysiology of myofascial TMD pain will be provided with a special reference to some of the unique features of the jaw muscles. We review the potential risk factors and neurobiological models to account for the transition from acute to persistent or dysfunctional pain and the consequences of myofascial TMD pain on motor function.

Special Characteristics of the Jaw Musculature

In the past, the dental and medical literature has paid relatively little attention to the structural and functional differences between the jaw musculature and limb or trunk muscles. Particularly with regard to the heterogeneous intramuscular activation capability of the muscles, possible implications of these differences for the development of localized myofascial TMD pain have been largely neglected.

The classical understanding of the activation of an individual muscle is based on a so-called homogeneous activation: the force increase in an individual muscle is explained by sequential recruitment of its motoneurons, which differ in size but receive the same synaptic input (so-called size principle) [25]. However, this model does not provide a satisfactory basis for explaining the origin of a generally assumed discrete muscular microtrauma caused by local strain, because the concurrent activation of all motoneurons of a specific size makes it difficult to generate localized strain in an individual muscle.

Conversely, recent findings showing the capability of the jaw musculature for heterogeneous activation [26–32] point to a plausible explanation of the clinical phenomenon of localized myofascial TMD pain. 'Heterogeneous activation' refers to the fact that the motoneurons of an individual muscle are divided into subpopulations. These subpopulations receive different synaptic input, i.e. they may be activated differentially. Such a 'functional compartmentalization' of the muscles makes localized strain within discrete muscle regions during specific motor tasks considerably more likely than a homogeneous activation. The key point here is to find out if myofascial TMD pain is uniquely associated with 'localized' painful spots and how the pain may spread or be referred to more extensive parts of the muscle. Nevertheless, it is a common clinical experience that distinct parts of the muscles are painful on palpation but techniques to differentiate between a localized painful spot and confluences of painful spots are obviously needed.

Additional support for this concept of localized muscle strain comes from the finding that the fibers of single motor units occupy only limited subvolumes of the jaw muscles [33]. This is in contrast to the single motor unit fibers of the extremity muscles, which are scattered in a 'mosaic pattern' over wide areas of the muscle cross-section. Furthermore, motor units of jaw muscles display clear directional properties [34, 35], i.e. they are preferentially activated at a specific force or movement direction. This approach provides a sound model for explaining the prolonged stereotypic activation of certain motor units (or small groups of motor units) up to functional exhaustion during specific motor tasks as it is assumed for the so-called Cinderella motor units [36–39]. The 'grouping' of muscle fibers to small fascicles provides the structural basis for such a selective recruitment behavior [33]. New findings from experiments on rats

confirm this idea: focal microlesions occur in the masseter following abnormal chewing strain [40] when the teeth of one jaw side are reduced in vertical height. (The possible meaning of the differential activation for localized myofascial TMD pain management will be discussed in the paragraph 'Occlusal splints').

These findings could point towards a greater susceptibility of jaw muscles to develop pain. It should also be considered, however, that fatigue studies on symptom-free non-TMD subjects generally suggest that jaw muscles are extremely well-equipped to resist the development of fatigue and muscle soreness [41, 42].

On the other hand, experimental studies with minor changes in the occlusion (artificial occlusal interferences) have shown that the susceptibility to develop some painful symptoms in the jaw muscles is explicitly higher in otherwise symptom-free individuals with a TMD history than in subjects without such a history [43, 44]. This could point to additional predisposing factors which determine the overall vulnerability of the masticatory muscles as it is conceptualized in the following section.

Risk Factors in the Pathogenesis of Myofascial TMD Pain

In analyzing the relationships between potential risk factors and the development of pain, it should be noted that the affected tissues may demonstrate a range of functional, structural and hormonal vulnerabilities. Together with the capability for heterogeneous activation of the jaw musculature, these partially unknown variables result in a variety of individual dispositions, which make it difficult to identify specific pain-triggering factors or biomechanical strain in individual patients. For this reason, myofascial TMD pain should be interpreted as a phenomenon determined by multiple factors [45]. The pain can also be influenced by continuous activation of descending motor pathways, as it might occur in the case of psychological distress or a hypervigilant disposition [46].

Modern biomedical concepts, therefore, distinguish between 3 types of risk factors [45, 46]:

- predisposing (e.g. structural, neuroendocrine, genetic);
- initiating (e.g. microtrauma and strain), and
- perpetuating (e.g. psychological, psychosocial, parafunctions).

The subdivision into predisposing, initiating and perpetuating factors is not conceptualized rigorously, however. For one particular individual, jaw muscle strain may be an initiating factor and psychological distress the perpetuating component; for another subject, the reverse may apply. Furthermore, it is essential to interpret this concept as an integral component of a comprehensive biopsychosocial model of pain (see later in this text) [47].

Microtrauma

In the past, numerous mechanisms have been considered as potential source of myofascial TMD pain. The most common models involve nociceptor pain, which is triggered by strain in the musculature. The pain can be promoted by a number of disposing factors. Microtrauma, local ischemia [48] or hypoperfusion [49] and their supposed structural and/or functional consequences, e.g. myofascial trigger point and postexercise muscle soreness, serve as the underlying pathophysiological model. This hypothesis assumes that at the end of a pathogenetic causal chain of events there is a release of endogenous algesic substances from tissue cells and afferent nerve fibers (e.g. glutamate, bradykinin, histamine, prostaglandin E_2, serotonin, potassium, adenine triphosphate, substance P, protons), which excite and/or sensitize muscle nociceptors (see also the chapter by Mense, pp 7–17).

It is interesting to note that the excitatory amino acid glutamate may initiate pain in muscle tissue without any sign of inflammation. A number of recent studies have tested the effects of intramuscular injections of glutamate and have shown that glutamate is associated with activation and sensitization of peripheral nociceptive afferent fibers in rats and with localized and referred pain sensations, accompanied by decreases in pressure pain thresholds in human subjects [50]. Moreover, N-methyl-D-aspartate receptor antagonists such as ketamine have analgesic and antiallodynic effects [51]. These observations, in addition to results from microdialysis studies, imply that glutamate may play a role in noninflammatory pain conditions as assumed to prevail in a broad spectrum of TMDs [52].

Parafunctions

Recent studies have consistently confirmed that self-reported tooth grinding and jaw clenching (bruxism) as well as other parafunctions are possible risk factors for TMDs [19, 53, 54]. However, the neurobiological relationship between parafunctions and myofascial TMD pain has still not been conclusively explained [55]. Curiously, patients with painful symptoms in the jaw muscles have less electromyographic (EMG) activity during sleep than do patients without painful symptoms [56]. Bruxism may, but does not necessarily, accompany jaw muscle pain. When pain associated with bruxism occurs, it is usually most pronounced in the morning [57]. The pain may be interpreted as a form of postexercise muscle soreness, although it demonstrates other characteristics than the soreness that occurs in the extremities [58]. In an experimental setting, intermittent muscle exertion (jaw clenching) with moderate or maximum force quickly leads to myofascial TMD pain. Eccentric muscle exertion under heavy loads, as assumed to occur in bruxism, may result in extensive muscle lesions [59], but this has so far not been shown in jaw muscles.

Occlusal Factors

It has been assumed for decades that changes in the dentition (tooth loss, restorative measures, orthodontic interventions, occlusal interferences) trigger new, nonadaptive (and perhaps nonadaptable) movement patterns, which may lead to neuromuscular imbalances (dysbalances) and, ultimately, to pain [60]. Epidemiological studies have shown, however, that the influence of occlusal factors with regard to the occurrence and prolongation of myofascial TMD pain plays a substantially lesser role than has been traditionally assumed [61]. Recent experimental evidence also disproved the belief that occlusal interferences cause muscle hyperactivity and subsequently pain in the jaw muscles in healthy subjects [62]. Although the role of occlusal factors may have been vastly overestimated in older pathophysiological models of myofascial TMD pain, it is appropriate to note that certain types of occlusion may have weak but statistically significant associations with TMD pain [63], but also that these associations may not be taken as a general justification or recommendation to perform irreversible and extensive occlusal therapy (see below).

Enhanced Muscle Activity at Rest

Another factor which has often been linked to the pathophysiology of myofascial TMD is the muscle activity as measured by EMG electrodes in the jaw muscles with the mandible in its rest or postural position [2]. However, the pathogenetic meaning of elevated jaw muscle activity at rest is unclear because if EMG changes are detected, and not all studies have been able to demonstrate this, they are only in the magnitude of a few microvolts which represent a very small percentage of the maximal output of these muscles. In a recent, well-controlled study [64], increased resting activity in the jaw muscles of orofacial pain patients was observed. Nonetheless, it is still unclear, whether this phenomenon, which is assumed to be the consequence of pain, may cause or contribute to additional pain in the affected muscles. Interestingly, Bodere et al. [64] also noted EMG changes in patients with neuropathic pain problems. This suggests that if EMG changes occur in painful conditions, they are not unique to musculoskeletal types of pain. Some authors suppose that an enhanced EMG activity at rest is a risk factor, acting like a classic conditioning effect (respondent conditioning) [65]. It has been argued that overactivation of single motor units (long-lasting recruitment) [66] as well as strain caused by overload of an entire muscle could be the source of muscle injury, i.e. myofascial TMD pain [59]. So far, however, no sustained firing motor units in resting jaw muscles with elevated rest activity could be found.

Neuroendocrine Factors

There are indications that endogenous or exogenous hormones, such as the estrogens and their influence on nerve growth factor and nociception [67], may

play an important role in the genesis of TMD pain. Recent studies have shown that injections of nerve growth factor into the masseter muscle cause long-lasting (weeks) muscle allodynia and pain associated with strenuous jaw movements, which seems to be more pronounced in women than in men [68, 69]. These new findings may offer an explanation for the long-known clinical observation supported by epidemiological studies that women, especially those of childbearing age, are more often affected by pain in the area of the jaw musculature than men (for further details, see the chapter by LeResche, pp 44–74).

Genetic Factors

A recent study [70] has demonstrated that patients with a genetic polymorphism of the enzyme catechol-O-methyltransferase show reduced enzyme activity, leading to an impaired degradation of the neurotransmitter dopamine. The resulting increased dopamine concentration causes a decrease in μ-opioid-receptor-dependent activation of certain brain regions (e.g. corpus amygdaloideum, nucleus accumbens, vermis cerebelli). A reduced function of the endogenous pain-inhibitory system in such individuals may be important for the development of chronic pain, like in painful TMDs (for additional details, see the chapter by Stohler, pp 236–247).

Neurobiological Models of Persistent Myofascial TMD Pain

In many patients, the course of myofascial TMD pain is not limited to a few days or weeks. Instead, myofascial TMD pain develops to persistent pain, and it continues with some fluctuations (intermittent) over several months, often up to years (persistent or dysfunctional). Peripheral and central mechanisms are supposed to contribute to the transition from acute to persistent pain states.

Peripheral Sensitization

The long-lasting sensitization of nociceptors usually closely depends on the presence and the concentration of sensitizing substances. These substances lead to threshold reductions and, due to the continuous stimulation of nociceptors, to an increase in the discharge frequency in the afferent fibers. They comprise prostaglandins, bradykinin and many others (see also the chapter by Mense, pp 7–17) which are released in states of trauma and inflammation. Additionally, pain is aggravated by ‘neurogenic inflammation’, i.e. by neuropeptides (such as substance P, calcitonin gene-related peptide, neurokinin A and vasoactive intestinal polypeptide) released from the nociceptors themselves, which cause vasodilatation and plasma extravasation. Sprouting of the nociceptive terminals can also contribute to the formation of long-lasting peripheral

sensitization. Sensitization of nociceptors is assumed to be the peripheral neurobiological basis of muscle tenderness (allodynia) and hyperalgesia [4]. Recent studies have further highlighted the effects of glutamate on peripheral nociceptive afferent fibers with respect to long-lasting sensitization and pharmacological properties [51, 71]. A clinical correlate of peripheral sensitization is pain on palpation and pain provoked by movement of the jaw.

Central Sensitization

The current opinion is that a strong burst or long-lasting nociceptive inflow from the periphery results in a range of long-term functional and structural changes and sensitization in the central nervous system (neuroplasticity). These processes, which are associated with long-lasting excitation of central nociceptive neurons, play a decisive role in the occurrence of so-called secondary (central) hyperalgesia, by which persistent pain may be maintained even without nociceptive information from the periphery [72]. Another factor for an enhanced excitability of trigeminal nociceptive neurons is a dysfunction of the descending pain inhibition triggered by continuous peripheral nociceptive inflow [48]. Finally, since descending pain-facilitatory pathways have been described, the question arises if persistent pain may be due to or maintained by an imbalance between inhibitory and facilitatory descending pathways [73]. At present, there is no simple clinical test which can accurately differentiate between the manifestation of peripheral and central sensitization in muscles and it may be most useful to think that both mechanisms may be at work in persistent myofascial TMD pain.

The Motor System and Myofascial TMD Pain

Pain and Electromyographic Activity at Rest

The traditional pain-spasm-pain hypothesis proposes a mutually reinforcing relationship between pain and muscle hyperactivity due to pain-induced, reflexively sustained tonic contraction of the injured muscle, thus setting up a vicious cycle [74]. In experimental animal models, however, it could be shown that a long-lasting acute inflammatory nociceptive input from limb muscle did not increase resting activity in the compromised muscle [75]. The γ-motoneurons, which are thought to be responsible for an enhancement of the resting activity [76], showed a pronounced inhibition. In human experimental studies, no long-lasting increases in EMG activity with the jaw at rest could be found [77, 78]. Conversely, injection of algesic substances in deep craniofacial tissues, i.e. the temporomandibular joints of the rat, elicited strong facilitation of the jaw-opening and jaw-closing muscles. This phenomenon confirms the existence of excitatory

pathways to the α-motoneurons under acute conditions with strong noxious inputs and can be explained as a 'splinting' effect to protect the injured structures. Increased resting activity under persistent pain conditions [64] could however be the result of a dysfunctional state of the ascending reticular activating system [58]. In sum, there is no convincing scientific evidence that elevated resting activity, as it can be observed under certain clinical pain conditions, contributes substantially to the initiation, perpetuation or disposition of myofascial TMD pain.

Pain and Static or Dynamic Electromyographic Activity

The current understanding of the interrelationship between pain and motor reactions assumes that nociceptive afferents from the jaw musculature influence the activity of the motoneurons by inhibitory and excitatory interneurons. Supposedly, this occurs in a reciprocal manner during muscle contraction (e.g. mastication): pain-related inhibition of the activity by the agonists results in increased activity (cocontraction) in the antagonists. Hence, painful opening of the mandible is associated with a slight increase in the activity of the jaw closers (antagonists), as could be shown in several human experimental studies [79, 80]: when the jaw is closed, the activity of the jaw closers (agonists) is reduced and some activity can be detected in the jaw openers. The maximum contraction force in intercuspation is thereby diminished, whereas jaw opening is reduced in its amplitude and speed. The accompanied limitation of jaw movement ('splinting effect') is interpreted as a reflex-driven adaptation mechanism to protect the affected anatomical structures and to reduce the existing pain (pain adaptation model [81]). This motor behavior corresponds fairly well with the clinical features found in TMD patients [for a review, see 2]. Nociceptor stimulation of other segmental structures, such as the dental pulp, the skin and the temporomandibular joints, is also thought to trigger similar sensorimotor adaptations. In conclusion, the available data suggest that static and dynamic motor activities are changed by the presence of pain. Hence, aberrant motor behavior (neuromuscular dysbalances) observed in patients are in most cases likely to be the consequence and not the cause of pain [2]. Nonetheless, the long-term effect of pain-adapted motor function is not known. Furthermore, no scientific data are available that could support the speculation that segmental adaptation in motor function spreads the regional pain by a muscular chain reaction [82].

Hypothesis for Transition from Acute to Dysfunctional Pain Conditions

In most cases, it can be argued that a peripheral 'lesion' precipitates the central nervous phenomena, e.g. in form of microtrauma, overload, overactivation

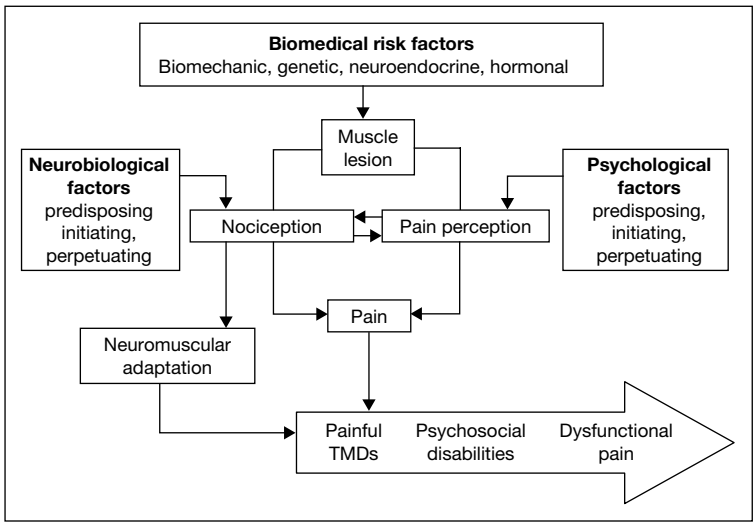

Fig. 1. Model for biopsychological aspects of persistent and dysfunctional myofascial TMD pain.

and/or muscle fatigue. When the peripheral lesion fails to heal, a prolonged phase, i.e. persistent pain, ensues. General vulnerability of the patient, due to genetic predisposition, hormonal factors, behavioral habits or failed therapy, may be an underlying factor [47]. Depending on the pain-coping behavior (adaptive or maladaptive), this state can finally lead to a dysfunctional pain condition (fig. 1). Taxonomies which define the transition from acute to dysfunctional pain by a stringent time course (e.g. 3 or 6 months) do not reflect the clinical reality satisfactorily, as already mentioned at the outset.

Consequences of Persistent Myofascial TMD Pain

Persistent myofascial TMD pain is usually accompanied by psychosocial and behavior-related consequences, e.g. restrictions in the performance of daily activities, reduced feeling of well-being or loss of motivation [83]. It is noticeable that such psychosocial disabilities are usually more strongly pronounced in patients with additional or concomitant pains located outside the region of the head-face and neck than in individuals who experience pain limited solely to the head, face and sometimes the neck [10]. Furthermore, numerous nonspecific physical symptoms, e.g. insomnia or dizziness, may be found in patients with dysfunctional myofascial TMD pain. Dysfunctional pain conditions and other diseases are interpreted as multidimensional experiences characterized and maintained by the interaction of biomedical, social, cultural, economic and behavioral factors [84].

Diagnostic Process

Thus far, no scientifically confirmed all-embracing hypothesis exists regarding the etiology of myofascial TMD pain. Therefore, the diagnostic process relies on the description of symptoms, i.e. the symptomatology, and should be based on the following procedures:

(1) the symptoms reported by the patients (pain-related history);
(2) the clinical evaluation, preferably according to the RDC/TMD [7]; in addition to a pain-related interview, the use of standardized pain questionnaires and pain drawing is recommended.

The clinical evaluation consists of the measurement of the mandibular mobility (and pain that may occur during movement) and the palpation of the palpable masticatory (and, if needed, cervical) musculature to determine the presence of pain. The latter should be measured manually but with attempts to apply predefined loads, e.g. 10 N for the temporalis and masseter muscles [7]. The application of pressure algometers is unusual for this purpose.

A recommendation for standardized diagnosis of temporomandibular pain, developed by the Interdisciplinary Working Group for Orofacial Pain within the German Association for the Study of Pain (DGSS), presents a step-by-step diagnostic concept that distinguishes between minimal, standard and extended diagnosis [85] (fig. 2).

In addition to the physical findings (axis I), pain-related psychosocial parameters (axis II) are to be evaluated. According to the RDC/TMD, within axis I, there are only two quite unspecific pain-related muscle 'diagnoses' ('myofascial pain' and 'myofascial pain with limited jaw opening') [7]. This accounts for the current understanding of myofascial TMD pain as a regional soft tissue pain syndrome. The proper diagnoses imply, of course, the exclusion of other types of jaw muscle pain, such as contractures, dystonia or myositis. However, these symptom-based diagnoses of myofascial TMD pain, which include acute and persistent forms, show little discriminatory power for other persistent muscle pain conditions, such as fibromyalgia syndrome or episodic tension-type headache. The use of pain drawings (whole body and face/head) may help to obtain a good understanding of the localization of the pain complaints and may facilitate the process of differential diagnosis, e.g. for the distinction between myofascial TMD pain and tension-type headaches [2].

The findings in axis II subsequently influence the diagnostic and therapeutic decision-making. In the case of increased pain-related psychosocial impairment of the patient, they lead to an interdisciplinary approach that includes a cooperation with a psychotherapist experienced in pain diagnosis and management. The extent of the psychosocial impairment also offers an early reference point (in contrast to the late one, namely, the therapeutic failure) for dysfunctional

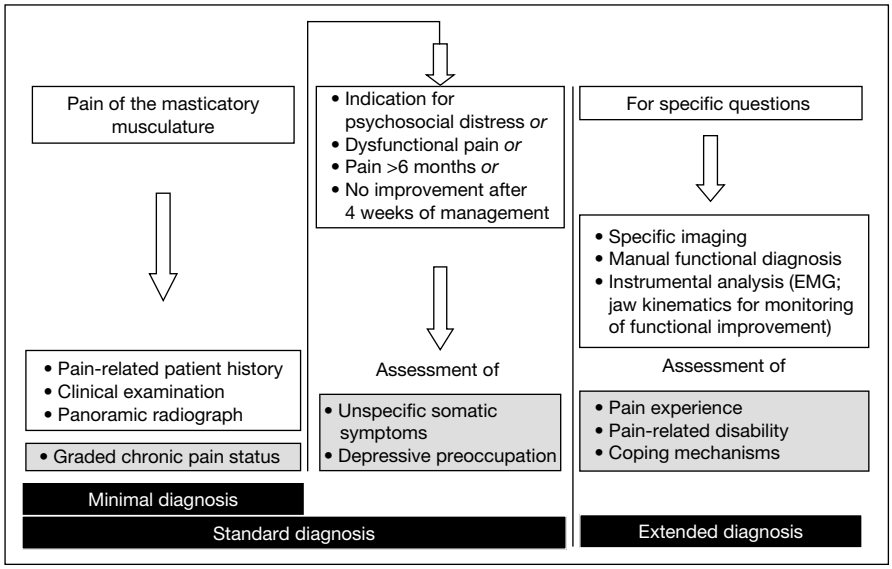

Fig. 2. Flowchart describing step-by-step procedure in the diagnostic process. Shaded panels represent axis II assessments.

pain courses, which may only be influenced to a limited degree (so-called dysfunctional pain) [83, 86].

Differential Diagnoses

Fibromyalgia Syndrome

Fibromyalgia is a common medical condition characterized by widespread pain and sensitivity to palpation at multiple anatomically defined tissue body sites. It is often accompanied by depression, insomnia and dysfunction of the autonomic nerve system. The diagnosis is typically based on the presence of pressure pain in at least 11 of 18 defined body locations, whereby the jaw musculature and temporomandibular joints are not included among these locations. Muscle pain is now believed to be primarily due to central nervous system neurosensory amplification of nociception in general and not specifically to muscle pathology [87]. Fibromyalgia can be distinguished from persistent myofascial TMD pain only by the patient history, the general physical examination and/or pain drawings showing all pain locations of the patient.

Episodic Tension-Type Headache

Episodic tension-type headache is characterized by temporal, frontal or occipital dull nonpulsing pain [88]. The pericranial musculature of a large majority of the patients is tender to pressure (65%). Increased excitability of the central nervous system generated by repetitive and sustained pericranial myofascial input may be responsible for the transformation of episodic tension-type headache into the chronic form [89]. Temporally localized episodic tension-type headache with the temporal muscle(s) sensitive to palpation cannot be distinguished from myofascial TMD pain of these muscles.

Myositis

Myositis is an acute ailment characterized by general inflammation of the affected muscle and soft tissue. The muscle, which is restricted in its function, exhibits pressure pain and swelling. The most common form of myositis found in the area of the jaw muscles is myositis ossificans traumatica, a rare, but benign heterotopic bone growth in a muscle (or its fibers) following acute trauma or repeated injury [90]. The information gained from the patient history usually allows making an appropriate diagnosis.

Other diseases that may be associated with jaw muscle pain are:

- hypothyroidism;
- lupus erythematosus;
- scleroderma;
- temporal arteritis;
- Parkinson's disease;
- infection or trauma;
- dystonia.

Comorbidity

There is good evidence that the prevalence of headaches is high in patients with myofascial TMD pain (70%) [88]. Conversely 50% of headache patients show symptoms of myofascial TMD pain [91]. There is similar support for comorbidity between fibromyalgia and myofascial TMD pain [92]. However, the general question arises whether such a high prevalence represents a coexistence of different pathologies, or whether it reflects the inability of the diagnostic instruments to distinguish between these ailments. Another explanation for the high comorbidity could be that the different pain phenomena share common pathogenetic pathways, i.e. an increased excitability of the central nervous system as it is generally assumed in persistent pain conditions.

Conclusively, myofascial TMD pain can be regarded as regional manifestations of musculoskeletal disorders similar to those observed in other body regions. The painful local muscle disturbances are assumed to be associated with a variety of biophysiological risk factors (hormonal, neuroendocrine, genetic and biomechanical). No specific pain-triggering factor could be identified so far. Therefore, myofascial TMD pain should be interpreted as a phenomenon determined and influenced by a multitude of factors which will have obvious implications for the management of these problems.

Short Summary

Most myofascial TMD pains can be easily managed, and they are rather episodic in nature (intermittent; see previous sections). In a considerable number of pain patients, however, the pain persists over a long period of time despite therapeutic interventions. Pain that lasts for a long period of time may lead to substantial distress and associated psychosocial reactions. Structural changes in peripheral and central nervous nociceptive pathways may explain the neurobiological basis for these more refractory types of myofascial TMD pains. Since complex biopsychosocial interactions determine the development of these dysfunctional pain conditions, diagnostic instruments that consider somatic and psychological factors are needed to evaluate the patients' appropriate therapeutic demand. The RDC/TMD criteria are a valid diagnostic system, which meets these requirements to a reasonable extent, but where further development will follow as research is steadily accumulating.

Management

The following therapeutic options for the management of TMD patients have been recommended in the literature and/or current textbooks [46, 88, 93–96]. It has to be taken into consideration that in most clinical trials no clear distinction was made between patients with myofascial TMD pain and those with temporomandibular joint pain.

Biophysical Intervention

- Physical therapy [manual therapy, massage, transcutaneous electric nerve stimulation (TENS)].
- Physical self-treatment.
- Occlusal splint therapy.
- Acupuncture.

Pharmacological Intervention

- Nonsteroidal anti-inflammatory drugs, cyclobenzaprine, diazepam, tricyclic antidepressants, local anesthetics, botulinum toxin.

Psychological Intervention

- Patient education and counseling.
- Behavioral management (cognitive-behavioral therapy, biofeedback, progressive muscle relaxation).

In an attempt to update these recommendations for predominantly myofascial TMD pain patients, a literature search was carried out, which was strictly based on randomized controlled trials (RCTs).

Review of the Literature

Method

The following information sources and search strategies were used:

Sources: PubMed, Cochrane Library. Search strategy (PubMed): (masticatory muscle pain OR jaw muscle pain) AND therapy; TMD AND muscle pain AND therapy; myofascial pain AND masticatory muscles AND therapy. The search was limited to the period between January 1990 and December 2005. The identified publications were included if the following criteria were fulfilled: (1) predominantly myofascial muscle pain; (2) rating of the pain before and after intervention on numerical rating scale, visual analogue scale or comparable measures; (3) RCT; (4) 3 of 5 possible quality scores as proposed by Jadad et al. [97].

Pain reduction or a global symptom reduction not less than 50% as compared to the level before the start of the therapy was estimated as positive therapeutic outcome. This criterion was also fulfilled if verbal descriptors such as 'excellent', 'good' or 'no pain'/'light pain' were used to assess pain reduction. If possible, 'numbers needed to treat' (NNT = 1/absolute risk reduction) were determined, and 95% confidence intervals were calculated by the modified Wilson score method [98].

If no hit was yielded for a recommended intervention, the search was broadened by including meta-analyses, systematic reviews and articles on RCTs of combined TMD populations (i.e. not divided into myofascial TMD pain vs. temporomandibular joint pain). The search strategy for combined TMDs was: 'key word' AND (masticatory system OR temporomandibular disorders OR TMD OR craniomandibular disorders OR CMD) AND therapy.

If this search was also ineffective, the strategy was extended to meta-analyses and systematic reviews for muscle pain in other body regions, e.g. low back pain

['key word' AND (myofascial pain OR muscle pain OR low back pain) AND therapy; only the most current review/meta-anlysis was considered]. If no relevant article was found by this extension, the search was stopped at this point.

Notes. (1) A search was also conducted for 'flupirtine', a substance which is successfully applied in Germany and other countries for low back pain. (2) For physiotherapeutic interventions, manual therapy (i.e. manipulation or mobilization techniques) and massage were used as representative key words to structure the electronic search. Physiotherapeutic interventions are characterized by various 'philosophies' and, as a consequence, by different technical approaches. The common neurobiological path of any physical therapy [99] and the lack of scientific data for significant differences among the various techniques justifies a review of the various methods under these terms. (3) As the most extensively investigated electrophysical adjuvant in pain management [100], TENS was also admitted to the search. (4) Occlusal adjustment was not considered, because a recent meta-analysis did not recommend this intervention [101].

Results

Specific Search

Altogether, 15 relevant studies corresponding to the inclusion criteria were identified. Nine studies were placebo controlled, including 3 investigations with so-called placebo splints, i.e. palatal appliances without occlusion. In 3 studies, the controls were on a waiting list; 4 investigations compared different therapies, 1 looked for dosage effects of a therapy.

The following interventions were identified:

- occlusal splints (n = 7) [102–108];
- pharmacotherapy (n = 3) [109–111];
- botulinum toxin (n = 2) [112, 113];
- education and counseling (n = 1) [114];
- physical therapy (n = 1) [115];
- self-treatment (n = 2) [103, 105];
- acupuncture (n = 2) [106, 116];
- combined interventions (n = 4) [109, 110, 114, 115].

The study populations showed a significant heterogeneity. The span of the treated patients reached from 7 to 90 subjects. Mean pain scores at baseline amounted from 2.5 on a numerical rating scale (from 0 to 10) to 70 mm on a visual analogue scale (from 0 to 100 mm). Treatment time amounted from 1 application (botulinum toxin) to daily use over a period of 26 weeks (occlusal splints). In 2 studies, the splints were worn for 24 h, in 4 studies only at night. The presentation of the results allowed the calculation of the NNT for only 1 study.

Extended Search

The extended search used the following key words: for TENS 'transcutaneous electric nerve stimulation', for manual therapy 'manipulation OR mobilization', for

cognitive-behavioral therapy 'cognitive-behavioral therapy', for progressive muscle relaxation 'relaxation technique', for massage 'massage', for biofeedback 'biofeedback', for local anesthesia 'local anesthesia' and for flupirtine 'flupirtine'.

The search in the combined TMD populations revealed 1 meta-analysis for biofeedback [117] and 1 RCT for cognitive-behavioral therapy [118].

For manual therapy [119], massage [120], local anesthesia [121] and progressive muscle relaxation [122], a systematic review was found for each modality. The search for TENS revealed a meta-analysis [123].

The results of the RCTs, systematic reviews and meta-analyses regarding the therapeutic efficacy of the various interventions are summarized in table 1.

According to the international guidelines for cardiopulmonary resuscitation and emergency cardiovascular care [124], the following clinical recommendation classes were used:

(a) high recommendation: at least 1 RCT confirms therapeutic effectiveness;

(b) recommendation: efficacy is confirmed at least by 1 RCT for a nonspecific (myofascial) TMD population or by 1 meta-analysis/systematic review for muscle pain in other body regions, e.g. low back pain;

(c) restricted recommendation: although no evidence for the efficacy (under the presupposed criteria) could be found or only inconclusive data exist, clinical experience and expert opinion consider the intervention as effective.

Notes. If there are conflicting results in equivalent studies (e.g. 2 pros vs. 1 contra) and no pooling of data is possible, individual assessment of the studies decides the affiliation to the classes defined above.

The degree of recommendation of the specific interventions identified by the literature search is illustrated in table 2.

General Management Perspectives

The aim of the management for myofascial TMD pain is to relieve pain and to restore limited jaw mobility and/or impaired chewing function [125]. Hence, it is an integral part of contemporary oral rehabilitation. Fast pain relief should be attempted to avoid central nervous alterations in the nociceptive system (see the chapter by Sessle, pp 56–74) and to improve the chances of therapeutic success [126].

Therapeutic Options

Pharmacotherapy

Cyclobenzaprine and tricyclic antidepressants appear to be relatively effective medications for myofascial TMD pain patients [109, 127]. The efficacy of anticonvulsive drugs (diazepam, clonazepam) for jaw muscle pain is inconclusive

Table 1. Treatment effects of the interventions for the management of myofascial TMD pain

Intervention	Outcome				
	effective			inconclusive	not effective
	I	II	III		
Biophysical intervention					
Occlusal splints					
Local pain	X^P				
Widespread pain				X	
Manual therapy			X^S		
Massage			X^S		
TENS				X	
Physical self-therapy	X^S				
Acupuncture				X	
Pharmacological intervention					
Diazepam				X	
NSAID					X
Cyclobenzaprine	X^P				
Flupirtine				no data	
Tricyclic antidepressants		X^P			
Local anesthesia				X	
Botulinum toxin				X	
Psychological intervention					
Education/counseling/ cognitive-behavioral therapy	X^{S1}				
Progressive muscle relaxation			X^S		
Biofeedback		X^P			

I = Myofascial TMD pain; II = combined TMD; III = other body regions; NSAID = nonsteroidal anti-inflammatory drugs. Effective therapy may be better than placebo (superscript P) or good or better than standard therapy (superscript S).

[1]It is supposed that the effect of education, counseling and cognitive-behavioral therapy is not essentially related to the different painful TMD subgroups.

[109, 110]. In the case of an unclear genesis of the myofascial TMD pain (possible absence of inflammatory components [52]) and considering the known side effects of nonsteroidal antirheumatic drugs, cyclobenzaprine (Flexeril®) is suggested as a medication of first choice [109]. Meta-analyses which confirm the efficacy of this drug for other muscle-related pain conditions support this view [128, 129]. Cyclobenzaprine and flupirtine (Katadolon®) are character-

Table 2. Degree of recommendation for various interventions

Intervention	Outcome		
	high recommendation	recommendation	restricted recommendation
Biophysical intervention			
Occlusal splints			
Local pain	X		
Widespread pain		X	
Manual therapy		X	
Massage		X	
TENS			X
Physical self-therapy	X		
Acupuncture		X	
Pharmacological intervention			
Diazepam			X
NSAID			X
Cyclobenzaprine	X		
Flupirtine			X
Tricyclic antidepressants		X	
Local anesthesia			X
Botulinum toxin			X
Psychological intervention			
Education/counseling/ cognitive-behavioral therapy	X[1]		
Progressive muscle relaxation		X	
Biofeedback		X	

[1]It is supposed that the effect of education, counseling and cognitive-behavioral therapy is not essentially related to the different painful TMD subgroups.

ized by both analgetic and muscle-relaxant effects. RCTs which confirm the efficacy or effectiveness of flupirtine for the musculature are lacking thus far.

In persistent pain conditions, tricyclic antidepressants provide an effective pharmacological treatment for jaw muscle pain, probably due to the multitude of mechanisms, e.g. serotonergic, noradrenergic and N-methyl-D-aspartate actions [127]. Nonsteroidal anti-inflammatory drugs, in contrast, demonstrate little or no effect in persistent myofascial TMD pain conditions [110].

The diagnosis and severity of the pain should determine the use of these medications [130].

The short-term analgetic effect of local anesthetics is well known and a helpful ad hoc therapy to relieve intense pain. There is no evidence for a longer-lasting impact for this kind of intervention, however, this holds also for the so-called trigger point injections [121]. The use of botulinum toxin is inconclusive because there are conflicting data for the therapeutic effect in the masticatory system [112, 113]. It is a striking finding from the reviewed studies that NNT values are not reported, which otherwise is an important indicator of the magnitude of effect.

Notes. Clinical experience and expert opinion consider flupirtine as an effective medication for low back pain [131]. Drugs with muscle-relaxing effects have many additional effects; therefore, they cannot be used to imply pathophysiological causes. For example, flupirtine acts on potassium canals. It is supposed to contribute to pain reduction by stabilizing the membrane potential [132]. It combines analgetic muscle-relaxant and neuroprotective properties.)

Occlusal Splint Therapy

In contrast to a previous investigation [108], specific effects of occlusal splints were detected in 2 placebo-controlled trials with a myofascial TMD pain population [102, 104]. A further study controlled by a waiting list confirmed this result [105].

An investigation by Raphael and Marbach [104], which excluded a subgroup with widespread pain (presumably to a high degree dysfunctional pain patients), indicates that uncomplicated TMD patients with regional myofascial TMD pain may respond favorably and in a specific way to splint therapy. The NNT calculated for the study of Ekberg et al. [102] was 2.3 (95% confidence interval: 1.7–4.5), indicating that almost 3 patients with myofascial TMD pain will have to be treated before 1 of them experiences at least 50% pain relief. Presumably, the number needed to harm value is very high for oral appliances, at least when splints are worn 24 h a day for an extended period of time or when permanent positional changes of the mandible are attempted. A new type of oral appliance, the so-called nociceptive trigeminal inhibitory splint which is only placed on the upper incisors has not shown superior results compared to conventional splints, and concerns for unwarranted side effects in the occlusion have been voiced [133].

Specific effects depending on the splint design could not be verified. Nocturnal use of the appliances seems to be sufficient to elicit the desired therapeutic effects [102, 104].

There are several hypotheses for the effectiveness/efficacy of occlusal splints, including: (1) induction of behavioral and/or cognitive changes [134] and (2) reorganization of intramuscular recruitment patterns by temporary changing of the position of the mandible and thereby unloading of strained muscle regions [135, 136]. Whereas behavioral and cognitive changes can hardly explain

a therapeutic effect while the splints are incorporated during the night, there is experimental evidence for a variation in the intramuscular recruitment pattern after positional changes of the mandible [137, 138]. The proposed biomedical model for the effects of splint treatment hypothesizes that any temporary positional change (within a physiological range) might be useful for a regional pain reduction as far as local painful events are the source of myofascial TMD pain. The physiological basis of this concept is the heterogeneous activation capability of the musculature. However, this hypothesis should not be overemphasized at this point in time; further investigations are needed to validate this theory.

The fact that occlusal splints and occlusal adjustment therapy result in a comparable outcome [139] confirms that no invasive interventions are required for a successful management of patients with myofascial TMD pain. Irreversible positional changes of the mandible by occlusal adjustment are critical in these patients, because pain-related motor adaptations are likely to alter the intercuspal position as well as the reference position chosen for occlusal adjustment [140].

Physical Therapy

No study could be found which confirmed the efficacy of physical therapy (interpreted as the exertion of external influence on the body by physical principles, including all kinds of physical stimuli, e.g. pressure, movement, warmth, coldness, radiation, electricity) for myofascial TMD pain. Manual therapy and massage, however, are temporarily effective interventions for low back pain as shown by meta-analyses [119, 120]. On the basis of these results and according to a literature review by Feine and Lund [141], the following conclusion for the therapeutic efficacy of physical therapies may be drawn:

(1) patients' symptoms improve under these therapeutic modalities [115];
(2) all approaches show comparable effects, i.e. no therapy proved to be superior to another;
(3) within a period of 4 weeks, the therapeutic effect increases with a rising number of sessions (3 sessions/week); beyond this period of time, the result remains stable [115].

Overall, the efficacy of TENS is inconclusive [100]. However, (systematic) reviews for various body regions indicate that the effectiveness/efficacy depends to a large extent on the stimulated body region [123, 142] and the stimulation parameters [100]. Therefore, it may be an effective analgetic intervention in the orofacial region; however, this has not been investigated in controlled trials thus far.

Physical Self-Treatment

Self-treatment, combined with intensive education and counseling for directing the patient into the various self-management strategies characterized

by biomedical and behavioral elements [114, 143], seems to be an intervention that is as effective as occlusal appliances [103]. Less extensive strategies, however, do not show significant therapeutic effects [105].

Acupuncture

Inconclusive evidence is available suggesting that acupuncture may be as effective as occlusal splints and placebo acupuncture in treating myofascial TMD pain [106, 116]. On the basis of the results for occlusal splints, i.e. their supposed specific therapeutic effect, it may be concluded, however, that the effectiveness of acupuncture is not limited to the 'classic' acupuncture points. An alternative conclusion, namely that all these interventions are predominantly the outcome of nonspecific, i.e. behavioral changes, seems to be unlikely, but cannot be completely excluded.

Behavioral Management

Education of the patients is a crucial factor in managing myofascial TMD pain. A study by Michelotti et al. [114] showed that education and counseling, i.e. information about possible etiological relationships and management options, may effectively reduce pain. One essential task is to evaluate the patients' etiological beliefs, which are typically dominated by somatic associations, and to cautiously modify them if necessary. Patients have to learn to avoid risk factors, and they must be sensitized to abnormal mandibular postures or stereotypic oral (including occlusal) habits associated with their myofascial TMD pain. Daily parafunctional habits can often be influenced by the patient's self-control [46]. Education and counseling (e.g. modifying inappropriate beliefs, stress reduction, training in self-management of symptoms) represent biobehavioral interventions which can be delivered routinely by dentists, physicians and dental hygienists [11]. A study by Dworkin et al. [118] has demonstrated that minimal cognitive-behavioral interventions and management as usually delivered by dentists and dental hygienists showed approximately the same outcome in pain relief after the therapeutic phase. After 1 year of follow-up, however, the cognitive-behavioral group displayed significantly lower pain ratings and pain-related interferences as compared to the usual-care group. This emphasizes the long-term effectiveness of cognitive-behavioral interventions.

Several studies have shown that the chance of therapeutic success for patients with myofascial TMD pain increases when behavior-related factors are considered in the management regime [117, 118, 122]. Results from a meta-analysis [117] have underscored the positive effect of biofeedback on patients with myofascial TMD pain. These findings offer an explanation why in a study over an observation period of 6 months a therapy that combined occlusal splints and biofeedback was substantially more effective than the use of either intervention

method alone, particularly with regard to pain reduction [144]. Relaxation techniques, including progressive muscle relaxation, are also an effective intervention as far as chronic back pain is considered [122].

In conclusion, various interventions result in a comparable treatment outcome for myofascial TMD patients.

Selection of Management Strategies

The selection of appropriate interventions is influenced by a proper assessment using valid 2-axis diagnostic instruments, such as RDC/TMD criteria, which provide information about the complexity of the case.

Several additional questions influence the development of therapeutic strategies and must be solved on an individual basis:

What Are Diagnosis-Relevant Therapeutic Options for Fast Pain Relief?

Fast pain relief, in a neurobiological sense, means the reduction of persistent nociceptive signals from the periphery. It has to be borne in mind that the 'pain' phenomenon embraces somatosensory and psychological dimensions which have different sequelae for acute, persistent and dysfunctional pain conditions. It can be assumed that biomedical intervention (pharmacotherapy, occlusal appliances, physical therapy), whose effects are thought to reduce nociceptive afferent input to the central nervous system, act faster than behavioral interventions (this notion is strengthened by an investigation of Turk et al. [144]), which presumably work more slowly, using rather indirect pathways to reduce 'pain'. Hence, behavioral interventions seem to be less suitable for fast pain relief of acute or persistent pain conditions.

What Are the Least Invasive and Safest Interventions Regarding the Prospective Therapeutic Results?

This aspect has to be discussed in association with the demand for fast pain relief (avoiding central nervous alteration). In particular, intensity and/or duration of pain as well as pain-related patient behavior must be considered with regard to additional pharmacotherapy, which might show more side effects than concurrent biomedical interventions but has the fastest impact on nociception. In analogy with the NNT, the numbers needed to harm could be a useful measure also in dentistry.

What Are the Patients' Preferences?

Knowledge of the patients' preferences is important for an adequate management of individual pain conditions [145]. It would not be prudent, for

example, to persuade the patient to an intervention if she/he is not convinced that the intervention would be appropriate for her/him.

What Kind of Therapeutic Options Are Available?

The availability of treatment options is typically limited; in the case of acupuncture or biofeedback, for instance, it depends on the individual expertise of the dentist and it needs special instrumentation, which may not be available in every dental office or clinic. In addition, the pattern of health insurance companies influences the choice of interventions.

What Kinds of Interventions Are Needed Simultaneously to Achieve Long-Running Reduction of the Symptoms?

More often, long-lasting relief of symptoms in patients may be achieved to a higher degree by the simultaneous integration of cognitive-behavioral management and somatically oriented interventions than by exclusively relying on somatic or behavioral treatment [144].

What Are the Costs of the Therapeutic Options?

The various biomedical interventions have largely the same effect, but differ in costs. Among others, cost-effectiveness may be modified depending on the patients' country of residence; e.g., oral splints might be more cost-effective than acupuncture or physiotherapy in one country, in another country the reverse could be true.

Depending on the diagnosis and the individual demand, the therapeutic options should be carefully selected for the initial treatment phase, which usually lasts 4 weeks. After reviewing the initial response, modifications in the therapeutic options will be made if necessary (fig. 3).

The majority of myofascial TMD pain patients have a good prognosis, and they respond favorably to therapeutic interventions. Various biomedical treatment modalities are characterized by a comparable therapeutic effectiveness. Particularly when dealing with dysfunctional pain patients, however, interventions restricted to somatic complaints often fail; this is reflected in many patients' dissatisfaction with the therapeutic results [146]. Since RCTs about the efficacy and effectiveness of various treatment modalities for myofascial TMD pain are lacking, interventions should essentially be based on standards that are common practice for comparable musculoskeletal complaints in other areas of the body, such as low back pain. Interdisciplinary and multimodal therapeutic strategies, which take the pain-related psychosocial impairments of the pain patients into consideration, are indispensable in dysfunctional pain [147]. In most cases, additional therapy delivered by a psychotherapist is a conditio

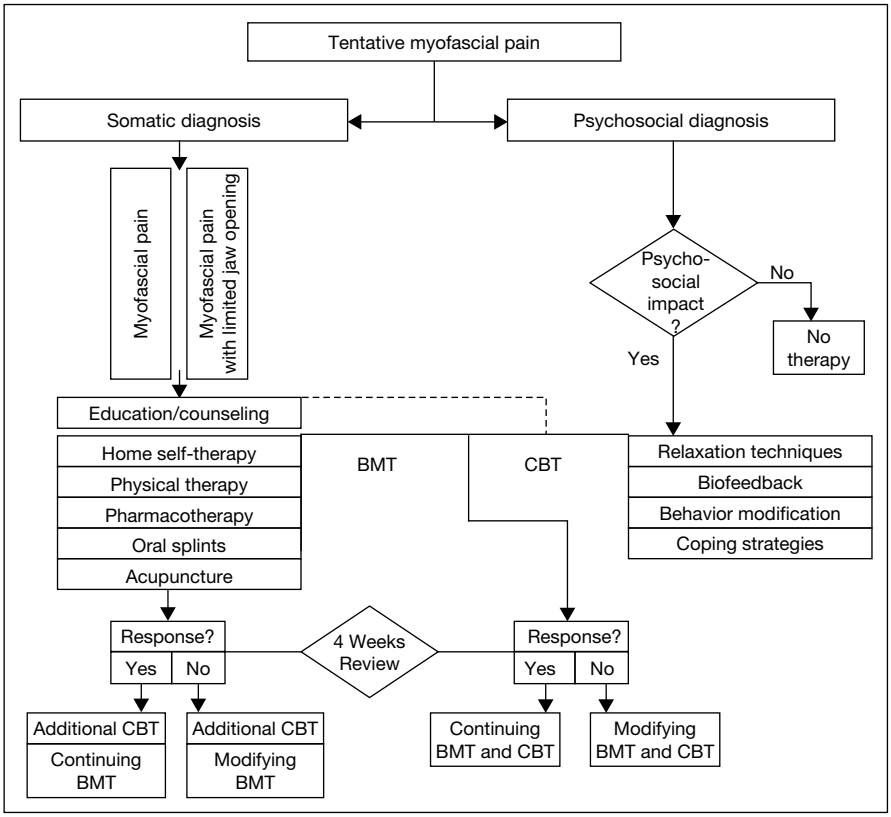

Fig. 3. Graduated decision-making for the management of myofascial TMD pain, based on a 2-axis diagnostic system. BMT = Biomedical treatment; CBT = cognitive-behavioral treatment. The dotted line refers to shared components of both CBT and education/counseling. The most important point here may be that all patients may require a 'battery' of modalities: some may require much more CBT than others; this is estimated from the psychosocial evaluation.

sine qua non. Noninvasive, reversible management strategies should always be given priority to invasive, irreversible approaches [46, 148].

References

1 Okeson JP: Management of Temporomandibular Disorders and Occlusion. St. Louis, Mosby, 2003.

2 Svensson P, Graven-Nielsen T: Craniofacial muscle pain: review of mechanisms and clinical manifestations. J Orofac Pain 2001;15:117–145.

3 Wright EF: Referred craniofacial pain patterns in patients with temporomandibular disorder. J Am Dent Assoc 2000;131:1307–1315.
4 Mense S, Simons DG: Muscle Pain: Understanding Its Nature, Diagnosis, and Treatment. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 253–259.
5 Hodges JM: Managing temporomandibular joint syndrome. Laryngoscope 1990;100:60–66.
6 Dworkin SF, Huggins KH, Wilson L, Mancl L, Turner J, Massoth D, LeResche L, Truelove E: A randomized clinical trial using research diagnostic criteria for temporomandibular disorders-axis II to target clinic cases for a tailored self-care TMD treatment program. J Orofac Pain 2002;16: 48–63.
7 Dworkin S, LeResche L: Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord Facial Oral Pain 1992;6:301–355.
8 Türp JC, Kowalski CJ, O'Leary N, Stohler CS: Pain maps from facial pain patients indicate a broad pain geography. J Dent Res 1998;77:1465–1472.
9 Türp JC, Kowalski CJ, Stohler CS: Temporomandibular disorders – Pain outside the head and face is rarely acknowledged in the chief complaint. J Prosthet Dent 1997;78:592–595.
10 Türp JC, Kowalski CJ, Stohler CS: Greater disability with increased pain involvement, pain intensity and depressive preoccupation. Eur J Pain 1997;1:271–277.
11 Dworkin SF: Behavioral characteristics of chronic temporomandibular disorders: diagnosis and assessment; in Sessle BJ, Bryant PS, Dionne RA (eds): Temporomandibular Disorders and Related Pain Conditions. Seattle, IASP Press, 1995, pp 175–180.
12 Woolf CJ: Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140:441–451.
13 Yap AU, Dworkin SF, Chua EK, List T, Tan KB, Tan HH: Prevalence of temporomandibular disorder subtypes, psychologic distress, and psychosocial dysfunction in Asian patients. J Orofac Pain 2003;17:21–28.
14 Rudy TE, Turk DC, Zaki HS, Curtin HD: An empirical taxometric alternative to traditional classification of temporomandibular disorders. Pain 1989;36:311–320.
15 List T, Dworkin SF: Comparing TMD diagnoses and clinical findings at Swedish and US TMD centers using research diagnostic criteria for temporomandibular disorders. J Orofac Pain 1996;10:240–253.
16 Vollaro S, Michelotti A, Cimino R, Farella M, Martina R: Studio epidemiologico su un gruppo di pazienti con disordini craniomandibolari: analisi dei dati e delle caratteristiche cliniche. Minerva Stomatol 2001;50:9–14.
17 LeResche L: Research diagnostic criteria for temporomandibular disorders; in Fricton JR, Dubner R (eds): Orofacial Pain and Temporomandibular Disorders. New York, Raven Press, 1995, pp 189–195.
18 List T, Wahlund K, Wenneberg B, Dworkin SF: TMD in children and adolescents: prevalence of pain, gender differences, and perceived treatment need. J Orofac Pain 1999;13:9–20.
19 Magnusson T, Egermarki I, Carlsson GE: A prospective investigation over two decades on signs and symptoms of temporomandibular disorders and associated variables: a final summary. Acta Odontol Scand 2005;63:99–109.
20 LeResche L, Mancl LA, Drangsholt MT, Saunders K, Korff MV: Relationship of pain and symptoms to pubertal development in adolescents. Pain 2005;118:201–209.
21 Goulet JP, Lavigne GJ, Lund JP: Jaw pain prevalence among French-speaking Canadians in Quebec and related symptoms of temporomandibular disorders. J Dent Res 1995;74:1738–1744.
22 Von Korff M, Dworkin SF, LeResche L, Kruger A: An epidemiologic comparison of pain complaints. Pain 1988;32:173–183.
23 Magnusson T, Egermark I, Carlsson GE: Treatment received, treatment demand, and treatment need for temporomandibular disorders in 35-year-old subjects. Cranio 2002;20:11–17.
24 Drangsholt MT, LeResche L: Temporomandibular disorder pain; in Crombie IK, Croft PR, Linton SJ, LeResche L, Von Korff M (eds): Epidemiology of Pain. Seattle, IASP Press, 1999, pp 203–233.
25 Henneman E, Somjen G, Carpenter DO: Functional significance of cell size in spinal motoneurons. J Neurophysiol 1965;28:560–580.

26 Belser UC, Hannam AG: The contribution of the deep fibers of the masseter muscle to selected tooth-clenching and chewing tasks. J Prosthet Dent 1986;56:629–635.
27 Blanksma NG, van Eijden TM, Weijs WA: Electromyographic heterogeneity in the human masseter muscle. J Dent Res 1992;71:47–52.
28 Blanksma NG, van Eijden TM: Electromyographic heterogeneity in the human temporalis and masseter muscles during static biting, open/close excursions, and chewing. J Dent Res 1995;74: 1318–1327.
29 Türp JC, Schindler HJ, Pritsch M, Rong Q: Antero-posterior activity changes in the superficial masseter muscle after exposure to experimental pain. Eur J Oral Sci 2002;110:83–91.
30 Murray GM, Phanachet I, Klineberg IJ: Electromyographic evidence for functional heterogeneity in the inferior head of the human lateral pterygoid muscle: a preliminary multi-unit study. Clin Neurophysiol 1999;110:944–950.
31 Tsuruyama K, Scott G, Widmer CG, Lund JP: Evidence for functional partitioning of the rabbit digastric muscle. Cells Tissues Organs 2002;170:170–182.
32 Widmer CG, Carrasco DI, English AW: Differential activation of neuromuscular compartments in the rabbit masseter muscle during different oral behaviors. Exp Brain Res 2003;150:297–307.
33 Tonndorf ML, Hannam AG: Motor unit territory in relation to tendons in the human masseter muscle. Muscle Nerve 1994;17:436–443.
34 McMillan AS, Hannam AG: Task-related behavior of motor units in different regions of the human masseter muscle. Arch Oral Biol 1992;37:849–857.
35 Phanachet I, Whittle T, Wanigaratne K, Murray GM: Functional properties of single motor units in inferior head of human lateral pterygoid muscle: task relations and thresholds. J Neurophysiol 2001;86:2204–2218.
36 Zennaro D, Laubli T, Krebs D, Klipstein A, Krueger H: Continuous, intermittent and sporadic motor unit activity in the trapezius muscle during prolonged computer work. J Electromyogr Kinesiol 2003;13:113–124.
37 Kadefors R, Forsman M, Zoega B, Herberts P: Recruitment of low threshold motor-units in the trapezius muscle in different static arm positions. Ergonomics 1999;42:359–375.
38 Armstrong TJ, Buckle P, Fine LJ, Hagberg M, Jonsson B, Kilbom A, Kuorinka IA, Silverstein BA, Sjogaard G, Viikari-Juntura ER: A conceptual model for work-related neck and upper-limb musculoskeletal disorders. Scand J Work Environ Health 1993;19:73–84.
39 Hägg GM: Static work and myalgia – A new explanation model; in Andersson PA, Hobart DJ, Danoff JV (eds): Electromyographical Kinesiology. Amsterdam, Elsevier Science, 1991, pp 141–144.
40 Bani D, Bani T, Bergamini M: Morphologic and biochemical changes of the masseter muscles induced by occlusal wear: studies in a rat model. J Dent Res 1999;78:1735–1744.
41 Plesh O, Meyerhoff DJ, Weiner MW: Phosphorus magnetic resonance spectroscopy of human masseter muscle. J Dent Res 1995;74:338–344.
42 Arima T, Svensson P, Arendt-Nielsen L: Experimental grinding in healthy subjects: a model for postexercise jaw muscle soreness? J Orofac Pain 1999;13:104–114.
43 Le Bell Y, Jamsa T, Korri S, Niemi PM, Alanen P: Effect of artificial occlusal interferences depends on previous experience of temporomandibular disorders. Acta Odontol Scand 2002;60: 219–222.
44 Le Bell Y, Niemi PM, Jamsa T, Kylmala M, Alanen P: Subjective reactions to intervention with artificial interferences in subjects with and without a history of temporomandibular disorders. Acta Odontol Scand 2006;64:59–63.
45 DeBoever JA, Carlson GE: Etiology and differential diagnosis; in Zarb GA, Carlsson GE, Sessle BJ, Mohl ND (eds): Temporomandibular Joint and Masticatory Muscle Disorders. Copenhagen, Munksgaard, 1994, pp 171–187.
46 Palla S: Myoarthropathien des Kausystems; in Palla S (ed): Myoarthropathien des Kausystems und orofaziale Schmerzen. Zürich, Klinik für Kaufunktionsstörungen und Totalprothetik, Zentrum für Zahn-, Mund- und Kieferheilkunde der Universität Zürich, 1998, pp 3–16.
47 Suvinen TI, Reade PC, Kemppainen P, Kononen M, Dworkin SF: 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 2005;9: 613–633.

48 Sessle BJ: The neural basis of temporomandibular joint and masticatory muscle pain. J Orofac Pain 1999;13:238–245.
49 Maekawa K, Clark GT, Kuboki T: Intramuscular hypoperfusion, adrenergic receptors, and chronic muscle pain. J Pain 2002;3:251–260.
50 Svensson P, Cairns BE, Wang K, Hu JW, Graven-Nielsen T, Arendt-Nielsen L, Sessle BJ: Glutamate-evoked pain and mechanical allodynia in the human masseter muscle. Pain 2003;101: 221–227.
51 Cairns BE, Svensson P, Wang K, Castrillon E, Hupfeld S, Sessle BJ, Arendt-Nielsen L: Ketamine attenuates glutamate-induced mechanical sensitization of the masseter muscle in human males. Exp Brain Res 2006;169:467–472.
52 Lam DK, Sessle BJ, Cairns BE, Hu JW: Neural mechanisms of temporomandibular joint and masticatory muscle pain: a possible role for peripheral glutamate receptor mechanisms. Pain Res Manag 2005;10:145–152.
53 Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT: Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). J Dent Res 2002;81:284–288.
54 Velly AM, Gornitsky M, Philippe P: Contributing factors to chronic myofascial pain: a case-control study. Pain 2003;104:491–499.
55 Lobbezoo F, Lavigne GJ: Do bruxism and temporomandibular disorders have a cause-and-effect relationship? J Orofac Pain 1997;11:15–23.
56 Arima T, Arendt-Nielsen L, Svensson P: Effect of jaw muscle pain and soreness evoked by capsaicin before sleep on orofacial motor activity during sleep. J Orofac Pain 2001;15:245–256.
57 Dao TT, Lund JP, Lavigne GJ: Comparison of pain and quality of life in bruxers and patients with myofascial pain of the masticatory muscles. J Orofac Pain 1994;8:350–356.
58 Svensson P: Pain mechanisms in myogenous temporomandibular disorders. Pain Forum 1997;6: 158–165.
59 Stauber WT, Smith CA: Cellular responses in exertion-induced skeletal muscle injury. Mol Cell Biochem 1998;179:189–196.
60 McCarroll RS, Naeije M, Kim YK, Hansson TL: Short-term effect of a stabilization splint on the asymmetry of submaximal masticatory muscle activity. J Oral Rehabil 1989;16:171–176.
61 Gesch D, Bernhardt O, Kirbschus A: Association of malocclusion and functional occlusion with temporomandibular disorders (TMD) in adults: a systematic review of population-based studies. Quintessence Int 2004;35:211–221.
62 Michelotti A, Farella M, Gallo LM, Veltri A, Palla S, Martina R: Effect of occlusal interference on habitual activity of human masseter. J Dent Res 2005;84:644–648.
63 Pullinger AG, Seligman DA, Gornbein JA: A multiple logistic regression analysis of the risk and relative odds of temporomandibular disorders as a function of common occlusal features. J Dent Res 1993;72:968–979.
64 Bodere C, Tea SH, Giroux-Metges MA, Woda A: Activity of masticatory muscles in subjects with different orofacial pain conditions. Pain 2005;116:33–41.
65 Knost B, Flor H, Birbaumer N, Schugens MM: Learned maintenance of pain: muscle tension reduces central nervous system processing of painful stimulation in chronic and subchronic pain patients. Psychophysiology 1999;36:755–764.
66 Zennaro D, Laubli T, Krebs D, Krueger H, Klipstein A: Trapezius muscle motor unit activity in symptomatic participants during finger tapping using properly and improperly adjusted desks. Hum Factors 2004;46:252–266.
67 Bjorling DE, Beckman M, Clayton MK, Wang ZY: Modulation of nerve growth factor in peripheral organs by estrogen and progesterone. Neuroscience 2002;110:155–167.
68 Svensson P, Cairns BE, Wang K, Arendt-Nielsen L: Injection of nerve growth factor into human masseter muscle evokes long-lasting mechanical allodynia and hyperalgesia. Pain 2003;104:241–247.
69 Castrillon E, Cairns BE, Svensson P: Long-lasting mechanical allodynia and hyperalgesia evoked by injection of nerve growth factor into the female masseter muscle. SASP Annu Meet adv Course, Stockholm, May 2006.
70 Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D: COMT val158met genotype affects μ-opioid neurotransmitter responses to a pain stressor. Science 2003;299:1240–1243.

71 Cairns BE, Svensson P, Wang K, Hupfeld S, Graven-Nielsen T, Sessle BJ, Berde CB, Arendt-Nielsen L: Activation of peripheral NMDA receptors contributes to human pain and rat afferent discharges evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2003;90: 2098–2105.
72 Ren K, Dubner R: Central nervous system plasticity and persistent pain. J Orofac Pain 1999;13: 155–163.
73 Suzuki R, Rygh LJ, Dickenson AH: Bad news from the brain: descending 5-HT pathways that control spinal pain processing. Trends Pharmacol Sci 2004;25:613–617.
74 Simons DG: Clinical and etiological update of myofascial pain from trigger points. J Musculoskelet Pain 1996;4:93–121.
75 Mense S, Skeppar P: Discharge behaviour of feline γ-motoneurones following induction of an artificial myositis. Pain 1991;46:201–210.
76 Johansson H, Sojka P: Pathophysiological mechanisms involved in genesis and spread of muscular tension in occupational muscle pain and in chronic musculoskeletal pain syndromes: a hypothesis. Med Hypotheses 1991;35:196–203.
77 Stohler CS, Zhang X, Lund JP: The effect of experimental jaw muscle pain on postural muscle activity. Pain 1996;66:215–221.
78 Svensson P, Graven-Nielsen T, Matre D, Arendt-Nielsen L: Experimental muscle pain does not cause long-lasting increases in resting electromyographic activity. Muscle Nerve 1998;21: 1382–1389.
79 Svensson P, Arendt-Nielsen L, Bjerring P, Bak P, Hjorth T, Troest T: Human mastication modulated by experimental trigeminal and extra-trigeminal painful stimuli. J Oral Rehabil 1996;23: 838–848.
80 Svensson P, Arendt-Nielsen L, Houe L: Muscle pain modulates mastication: an experimental study in humans. J Orofac Pain 1998;12:7–16.
81 Lund J, Donga R, Widmer C, Stohler C: The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. Can J Physiol Pharmacol 1991;69:683–694.
82 Lewit K: Chain reactions in disturbed function of the motor system. Man Med 1987;3:27–29.
83 Von Korff M, Ormel J, Keefe FJ, Dworkin SF: Grading the severity of chronic pain. Pain 1992;50:133–149.
84 Turk DC, Rudy TE, Kubinski JA, Zaki HS, Greco CM: Dysfunctional patients with temporomandibular disorders: evaluating the efficacy of a tailored treatment protocol. J Consult Clin Psychol 1996;64:139–146.
85 Türp JC, John M, Nilges P, Jürgens J, Ahlers MO, Böhner W, Busche E, Hugger A, Jakstat HA, Koch WH, Niederfeilner J, Paak S, Palatka P, Peschen-Rosin R, Schindler HJ, Sommer C, Sprotte G, Weissmann K, Wernze H: Schmerzen im Bereich der Kaumuskulatur und Kiefergelenke: Empfehlungen zur standardisierten Diagnostik und Klassifikation von Patienten. Schmerz 2000;14: 416–428.
86 Dahlström L, Widmark G, Carlsson SG: Cognitive-behavioral profiles among different categories of orofacial pain patients: diagnostic and treatment implications. Eur J Oral Sci 1997;105: 377–383.
87 Russell IJ: Fibromyalgia syndrome; in Mense S, Simons DG (eds): Muscle Pain: Understanding Its Nature, Diagnosis, and Treatment. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 289–337.
88 Okeson JP: Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management. Chicago, Quintessence, 1996.
89 Ashina S, Bendtsen L, Ashina M: Pathophysiology of tension-type headache. Curr Pain Headache Rep 2005;9:415–422.
90 Aoki T, Naito H, Ota Y, Shiiki K: Myositis ossificans traumatica of the masticatory muscles: review of the literature and report of a case. J Oral Maxillofac Surg 2002;60:1083–1088.
91 Schokker RP, Hansson TL, Ansink BJ: Craniomandibular disorders in patients with different types of headache. J Craniomandib Disord 1990;4:47–51.
92 Plesh O, Wolfe F, Lane N: The relationship between fibromyalgia and temporomandibular disorders: prevalence and symptom severity. J Rheumatol 1996;23:1948–1952.

93 Okeson JP: Bell's Orofacial Pains. Chicago, Quintessence, 2005.
94 Lund JP, Lavigne GJ, Dubner R, Sessle BJ: Orofacial Pain. From Basic Science to Clinical Management. Chicago, Quintessence, 2001.
95 Zarb GA, Carlsson GE, Sessle BJ, Mohl ND: Temporomandibular Joint and Masticatory Muscle Disorders. Copenhagen, Munksgaard, 1994.
96 Svensson P, Sessle BJ: Orofacial pain; in Miles TS, Nauntofte B, Svensson P (eds): Clinical Oral Physiology. Copenhagen, Quintessence Publishing, 2004, pp 93–139.
97 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
98 Bender R: Calculating confidence intervals for the number needed to treat. Control Clin Trials 2001;22:102–110.
99 Le Bars D: The whole body receptive field of dorsal horn multireceptive neurones. Brain Res Brain Res Rev 2002;40:29–44.
100 Sluka KA, Walsh D: Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. J Pain 2003;4:109–121.
101 Koh H, Robinson PG: Occlusal adjustment for treating and preventing temporomandibular joint disorders. Cochrane Database Syst Rev 2003;1:CD003812.
102 Ekberg E, Vallon D, Nilner M: The efficacy of appliance therapy in patients with temporomandibular disorders of mainly myogenous origin: a randomized, controlled, short-term trial. J Orofac Pain 2003;17:133–139.
103 Carlson CR, Bertrand PM, Ehrlich AD, Maxwell AW, Burton RG: Physical self-regulation training for the management of temporomandibular disorders. J Orofac Pain 2001;15:47–55.
104 Raphael KG, Marbach JJ: Widespread pain and the effectiveness of oral splints in myofascial face pain. J Am Dent Assoc 2001;132:305–316.
105 Wright E, Anderson G, Schulte J: A randomized clinical trial of intraoral soft splints and palliative treatment for masticatory muscle pain. J Orofac Pain 1995;9:192–199.
106 Johansson A, Wenneberg B, Wagersten C, Haraldson T: Acupuncture in treatment of facial muscular pain. Acta Odontol Scand 1991;49:153–158.
107 Schokker RP, Hansson TL, Ansink BJ: The result of treatment of the masticatory system of chronic headache patients. J Craniomandib Disord 1990;4:126–130.
108 Dao TT, Lavigne GJ, Charbonneau A, Feine JS, Lund JP: The efficacy of oral splints in the treatment of myofascial pain of the jaw muscles: a controlled clinical trial. Pain 1994;56:85–94.
109 Herman CR, Schiffman EL, Look JO, Rindal DB: The effectiveness of adding pharmacologic treatment with clonazepam or cyclobenzaprine to patient education and self-care for the treatment of jaw pain upon awakening: a randomized clinical trial. J Orofac Pain 2002;16:64–70.
110 Singer E, Dionne R: A controlled evaluation of ibuprofen and diazepam for chronic orofacial muscle pain. J Orofac Pain 1997;11:139–146.
111 Dao TT, Lund JP, Remillard G, Lavigne GJ: Is myofascial pain of the temporal muscles relieved by oral sumatriptan? A cross-over pilot study. Pain 1995;62:241–244.
112 Nixdorf DR, Heo G, Major PW: Randomized controlled trial of botulinum toxin A for chronic myogenous orofacial pain. Pain 2002;99:465–473.
113 von Lindern JJ, Niederhagen B, Berge S, Appel T: Type A botulinum toxin in the treatment of chronic facial pain associated with masticatory hyperactivity. J Oral Maxillofac Surg 2003;61:774–778.
114 Michelotti A, Steenks MH, Farella M, Parisini F, Cimino R, Martina R: The additional value of a home physical therapy regimen versus patient education only for the treatment of myofascial pain of the jaw muscles: short-term results of a randomized clinical trial. J Orofac Pain 2004;18:114–125.
115 De Laat A, Stappaerts K, Papy S: Counseling and physical therapy as treatment for myofascial pain of the masticatory system. J Orofac Pain 2003;17:42–49.
116 Goddard G, Karibe H, McNeill C, Villafuerte E: Acupuncture and sham acupuncture reduce muscle pain in myofascial pain patients. J Orofac Pain 2002;16:71–76.
117 Crider AB, Glaros AG: A meta-analysis of EMG biofeedback treatment of temporomandibular disorders. J Orofac Pain 1999;13:29–37.

118 Dworkin SF, Turner JA, Mancl L, Wilson L, Massoth D, Huggins KH, LeResche L, Truelove E: A randomized clinical trial of a tailored comprehensive care treatment program for temporomandibular disorders. J Orofac Pain 2002;16:259–276.
119 Assendelft WJ, Morton SC, Yu EI, Suttorp MJ, Shekelle PG: Spinal manipulative therapy for low back pain. Cochrane Database Syst Rev 2004;1:CD000447.
120 Furlan AD, Brosseau L, Imamura M, Irvin E: Massage for low-back pain. Cochrane Database Syst Rev 2002;2:CD001929.
121 Cummings TM, White AR: Needling therapies in the management of myofascial trigger point pain: a systematic review. Arch Phys Med Rehabil 2001;82:986–992.
122 Ostelo RW, van Tulder MW, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft WJ: Behavioural treatment for chronic low-back pain. Cochrane Database Syst Rev 2005;1:CD002014.
123 Khadilkar A, Milne S, Brosseau L, Robinson V, Saginur M, Shea B, Tugwell P, Wells G: Transcutaneous electrical nerve stimulation (TENS) for chronic low-back pain. Cochrane Database Syst Rev 2005;3:CD003008.
124 Guidelines: Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. I. Introcuction to the international guidelines 2000 for CPR and ECC. Circulation 2000;102 (suppl 1):1–11.
125 De Laat A: Kauwspieren. IX. Pijn in de kauwspieren. Ned Tijdschr Tandheelkd 1998;105:82–83.
126 Palla S: Grundsätze zur Therapie des myoarthropathischen Schmerzes. Schmerz 2002;16: 373–380.
127 Rizzatti-Barbosa CM, Nogueira MT, de Andrade ED, Ambrosano GM, de Barbosa JR: Clinical evaluation of amitriptyline for the control of chronic pain caused by temporomandibular joint disorders. Cranio 2003;21:221–225.
128 Browning R, Jackson JL, O'Malley PG, Tofferi JK: Cyclobenzaprine and back pain: a meta-analysis. Arch Intern Med 2001;161:1613–1620.
129 Tofferi JK, Jackson JL, O'Malley PG: Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. Arthritis Rheum 2004;51:9–13.
130 Sommer C: Pharmakologische Behandlung orofazialer Schmerzen. Schmerz 2002;16:381–388.
131 Wörz R, Müller-Schwefe G, Stroehmann I, Zeuner L, Zieglgänsberger W, Zimmermann M: Rückenschmerzen: Leitlinien der medikamentösen Therapie. MMW Fortschr Med 2000;142: 27–33.
132 Kornhuber J, Bleich S, Wiltfang J, Maler M, Parsons CG: Flupirtine shows functional NMDA receptor antagonism by enhancing Mg^{2+} block via activation of voltage independent potassium channels: rapid communication. J Neural Transm 1999;106:857–867.
133 Jokstad A, Mo A, Krogstad BS: Clinical comparison between two different splint designs for temporomandibular disorder therapy. Acta Odontol Scand 2005;63:218–226.
134 Kreiner M, Betancor E, Clark GT: Occlusal stabilization appliances: evidence of their efficacy. J Am Dent Assoc 2001;132:770–777.
135 Türp JC, Schindler HJ: Zum Zusammenhang zwischen Okklusion und Myoarthropathien: Einführung eines integrierenden neurobiologischen Modells. Schweiz Monatsschr Zahnmed 2003;113:964–977.
136 Schindler HJ, Rues S, Türp JC, Lenz J: Heterogeneous activation of the medial pterygoid muscle during simulated clenching. Arch Oral Biol 2006;51:498–504.
137 Van Eijden TM, Blanksma NG, Brugman P: Amplitude and timing of EMG activity in the human masseter muscle during selected motor tasks. J Dent Res 1993;72:599–606.
138 Schindler HJ, Türp JC, Blaser R, Lenz J: Differential activity patterns in the masseter muscle under simulated clenching and grinding forces. J Oral Rehabil 2005;32:552–563.
139 van der Glas HW, Buchner R, van Grootel RJ: Vergelijking tussen behandelingsvormen bij myogene temporomandibulaire dysfunctie. Ned Tijdschr Tandheelkd 2000;107:505–512.
140 Obrez A, Türp JC: The effect of musculoskeletal facial pain on registration of maxillomandibular relationships and treatment planning: a synthesis of the literature. J Prosthet Dent 1998;79: 439–445.
141 Feine JS, Lund JP: An assessment of the efficacy of physical therapy and physical modalities for the control of chronic musculoskeletal pain. Pain 1997;71:5–23.

142 Casimiro L, Barnsley L, Brosseau L, Milne S, Robinson VA, Tugwell P, Wells G: Acupuncture and electroacupuncture for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev 2005;4:CD003788.
143 Michelotti A, de Wijer A, Steenks M, Farella M: Home-exercise regimes for the management of non-specific temporomandibular disorders. J Oral Rehabil 2005;32:779–785.
144 Turk DC, Zaki HS, Rudy TE: Effects of intraoral appliance and biofeedback/stress management alone and in combination in treating pain and depression in patients with temporomandibular disorders. J Prosthet Dent 1993;70:158–164.
145 Sackett DL: Was ist evidenz-basierte Medizin? in Perleth M, Antes G (eds): Evidenz-basierte Medizin. München, MMV Medizin Verlag, 1998, pp 9–12.
146 Türp JC, Kowalski CJ, Stohler CS: Treatment-seeking patterns of facial pain patients: many possibilities, limited satisfaction. J Orofac Pain 1998;12:61–66.
147 Dworkin SF: The case for incorporating biobehavioral treatment into TMD management. J Am Dent Assoc 1996;127:1607–1610.
148 Health: National Institutes of Health Technology Assessment Conference Statement: management of temporomandibular disorders. J Am Dent Assoc 1996;127:1595–1603.

Dr. med. dent. Hans Jürgen Schindler
Hirschstrasse 105
DE–76137 Karlsruhe (Germany)
Tel. +49 721 93 33 713, Fax +49 721 35 85 46, E-Mail myo.schindler@t-online.de

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 124–152

Painful Arthrogenous Temporomandibular Disorders

Pathophysiology, Diagnosis, Management and Prognosis

Michel H. Steenks[a], *Alfons Hugger*[b], *Anton de Wijer*[a]

[a]Clinic for Temporomandibular Disorders and Orofacial Pain, Department of Oral-Maxillofacial Surgery, Prosthodontics and Special Dental Care, Division of Surgical Sciences, University Hospital Utrecht, Utrecht, The Netherlands; [b]Poliklinik für Zahnärztliche Prothetik, Westdeutsche Kieferklinik, Universitätsklinikum Düsseldorf, Düsseldorf, Germany

Abstract

Painful temporomandibular joint (TMJ) conditions can be specific and nonspecific. In the diagnostic process, the clinician has first to rule out specific conditions and conditions not related to the masticatory system. The nonspecific TMJ conditions lack a known pathophysiological substrate and are classified by clinical characteristics. Since arthralgia is a common symptom in many of the nonspecific clinical conditions, it is not a diagnostic entity. Patients usually show combinations of characteristics of nonspecific conditions (multiple conditions). Arthrogenous pain is often accompanied by myogenous pain due to functional integration of anatomical structures, and possibly due to common pathophysiological mechanisms, such as sensitization. Another common feature is the lack of well-identified risk factors. Trauma may initiate pain in the masticatory system that usually subsides spontaneously. The knowledge of the relation between degenerative and inflammatory processes is growing fast, hopefully providing better perspectives for patients. A comprehensive history, physical examination and radiological evaluation (panoramic radiograph) are key elements in arriving at a proper working diagnosis. With regard to management and prognosis in nonspecific chronic painful TMJ conditions, factors such as the course of the complaints, the result of earlier treatment, the type of the pain (nociceptive and/or neuropathic), the use of medication and aspects of chronicity, including a multitude of sources (biological, psychological), play a more prominent role than the nonspecific painful physical condition as such. The clinician can offer adequate patient education, pain medication, as well as orthopedic stability to the masticatory system, for instance by providing the patient with reversible occlusal splints and adequate physiotherapy. Explanation about the condition, reassurance and a homework program aiming at adequate coping, internal health locus of control and activation are basic ingredients of any management strategy. The long-term prognosis of chronic nonspecific painful TMJ conditions is good. Using this information

in the communication with the patient will help to change inadequate beliefs and cognitions into realistic perspectives.

Following the most frequently used definition, temporomandibular disorders (TMDs) is a collective term, embracing a number of clinical problems that involve the masticatory musculature, the temporomandibular joints (TMJs) and associated structures or both [1]. Comprehensive classifications regarding pain and headache are clinically based and follow the clinical decision-making process. They were originally initiated by the International Association for the Study of Pain [2] and the International Headache Society [3], and refined regarding TMDs in close cooperation between the International Headache Society and the American Academy of Orofacial Pain [1, 4].

The differential diagnosis of painful TMDs needs a broad perspective from the very first visit to avoid misdiagnosis. The concept of TMD diagnostic subgroups with different symptom profiles was introduced for research purposes and for clinical (descriptive, diagnostic and therapeutic) purposes. The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) focus on improving the definition of clinical samples for research purposes [5]. The clinical goals aim at the description of clinical characteristics and symptom profiles and consequent individualized therapy [6, 7]. The pre-1992 literature hardly presented precise definitions of the samples studied. In this chapter, the American Academy of Orofacial Pain classification is used to describe subgroups of painful TMJ conditions, since this classification is broader and allows for conditions not mentioned in the RDC/TMD axis I classification (e.g. dislocation, hypermobility, fracture, posterior disk displacement, ankylosis, neoplasia, growth disturbances). This is extremely important given the enormous variation in patients with painful arthrogenous TMD conditions. Clinical *conditions* is preferred over clinical *problems*, since it is a more neutral term [8].

Apart from these classification issues regarding painful arthrogenous axis I conditions, which were also reviewed in the context of the relation between osteoarthrosis and disk displacement by Stegenga [9], in clinical practice other aspects play an equally important role. Non-TMD conditions need to be excluded, and appropriate referral and evaluation of the obtained results are mandatory (fig. 1).

Furthermore, the differentiation between specific and nonspecific arthrogenous conditions is important [8, 10]. Management strategies highly depend on this dichotomy. Specific conditions are characterized by a known etiology, pathophysiological substrate and/or a systemic background, e.g. neoplasms, growth disturbances, syndromes (e.g. Ehlers-Danlos), rheumatic disease (e.g. juvenile

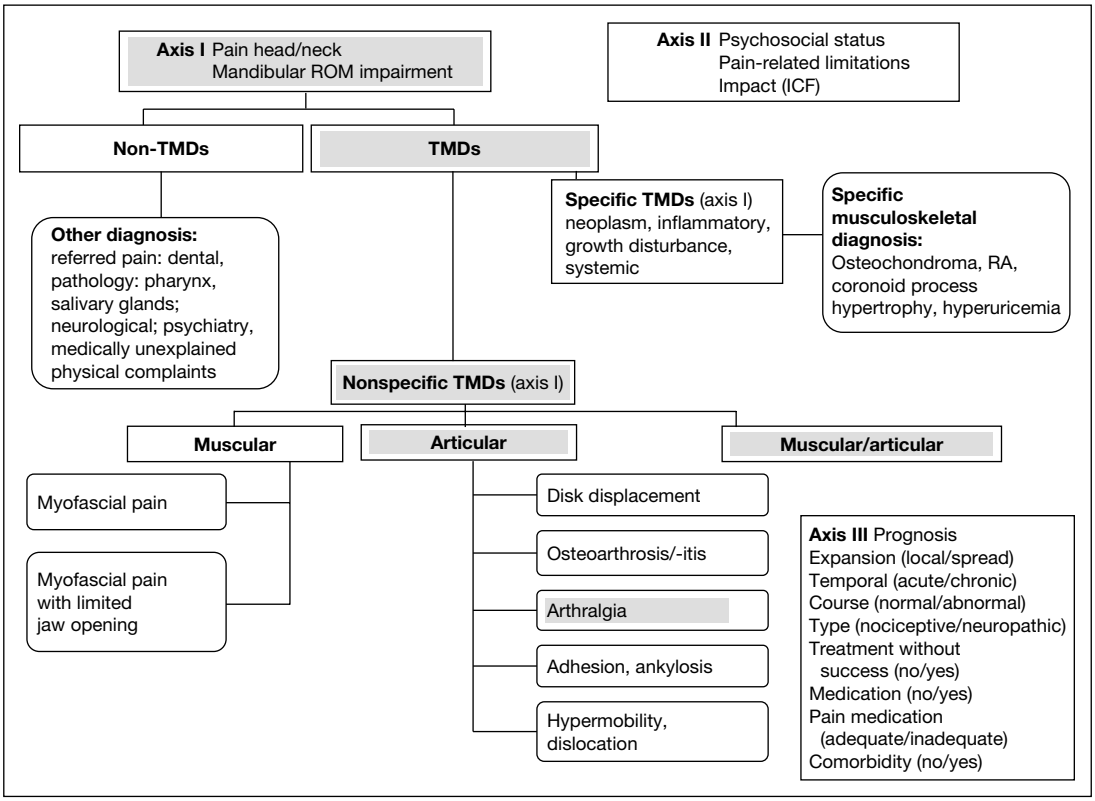

Fig. 1. Flowchart of the diagnostic process in suspected painful TMDs [10, 11]. Axis I represents the physical conditions. Non-TMDs = Other conditions presenting pain in the head and the neck, and mandibular range of motion (ROM) limitations; specific TMDs = conditions with a known substratum, e.g. neoplasms, growth disturbances, systemic disease; nonspecific TMDs = conditions related to overloading or trauma surpassing the adaptation capacity, generally divided into muscular and articular subgroups. Axis II represents psychosocial factors increasingly important when chronicity plays a more prominent role. Axis III comprises additional clinical considerations such as pain characteristics, medication and results of previous treatment, related to prognosis. ICF = International Classification of Functioning, Disability and Health (WHO); RA = rheumatoid arthritis.

idiopathic arthritis) or neurological disease (e.g. spinal muscular atrophy). They primarily need a specific treatment (e.g. medication, surgical procedure).

Nonspecific painful arthrogenous conditions, on the other hand, lack a known or measurable substrate. Their etiology is not well understood. Although nowadays much more is known about the inflammatory and degenerative aspects of painful TMJ conditions, this new information did not yet influence the choice

of modalities to a great extent, thereby challenging the idea that these nonspecific conditions are etiology-based diagnostic entities. Arthroscopy and synovial fluid analysis already provided more insight in the overlap of the painful arthrogenous entities described in figure 1 (see also the chapter by Kopp and Sommer, pp 28–43). So far, consensus exists on at least descriptive entities within presenting patient populations that are not totally mutually exclusive and also share some clinical characteristics [7]. Temporomandibular joint pain has also been differentiated as ligamentous pain, retrodiscal pain, capsular pain and arthritic pain [12]. These entities are difficult to differentiate from each other by clinical examination only. Arthralgia is an adequate umbrella term.

Another important distinction is between nociceptive pain and neuropathic pain (fig. 1). When both are present simultaneously, e.g. in chronic pain, or when sensitization may play a role, this can be conflicting for the clinician. The clinician also needs to be alert in case of a deviant course of the disorder, different from what is expected on the basis of the clinical experience regarding recovery of a condition and comorbidity. Crucial is the differentiation between acute and chronic pain. The pain literature indicates that the sooner therapy starts, the better the chances are to avoid the pain to become chronic. There is broad consensus that in chronic (e.g. arthrogenous) TMDs, a team approach in management is mandatory, in general consisting of a dentist, psychologist and physiotherapist.

This chapter is on painful TMJ conditions. Arthralgia may be present in the other nonspecific articular disorders as well (fig. 1). For this reason, and because of the diagnostic entity issues already discussed, we mostly focus on arthralgia, rather than to discuss the classical arthrogenous subgroups as such. When reading this chapter, one needs to realize that the articular and muscular group originates from the same nonspecific TMD group (fig. 1), in case of chronicity with probably some common pathophysiological characteristics [13–15]. This is one of the reasons for including a combined articular/muscular group. Other reasons are the mutual involvement of these anatomical structures and their functional integration. Much of the discussion regarding the clinical diagnoses or subgroups can be omitted when realizing that the term ‘diagnostic classification’ is too ambitious yet; rheumatologists cope with 4 out of 7 classification criteria to say a patient has rheumatoid arthritis. In this sense, the research *diagnostic* criteria are in fact research *classification* criteria.

Pathophysiology and Risk Factors

The TMJ is supplied by afferent and efferent sympathetic nerve fibers which are mainly carried in auriculotemporal, masseteric and deep posterior

temporal nerves of the trigeminal nerve [16]. The highest innervation exists in the posterior and lateral portions of the TMJ (retrodiscal tissue, synovial membrane, dense and loose fibrous tissues). Nerve fibers are normally absent in the intermediate (articulating) zone of the disk as well as in the mandibular and temporal surfaces of the joint [17]. The TMJ contains many free nerve endings, but few encapsulated specialized receptors (such as Ruffini, Golgi-Mazzoni and articular corpuscles) [18]. The afferents which supply these nonspecialized and specialized receptors are Aβ, Aδ and mainly C fibers [19]. The afferents are in one part low-threshold nonnociceptive with slowly or rapidly adapting properties for kinesthetic sense and motor control, and in the other part nociceptive slowly conducting which respond to noxious mechanical and chemical stimuli. Some afferents – also localized in the peripheral parts of the disk – show immunoreactivity for neuropeptides, such as substance P and calcitonin gene-related peptides, which are implicated in nociception and neurogenic inflammation [20]. Other perivascular fibers contain the neuropeptides vasoactive intestinal polypeptides and neuropeptide Y, which suggests an autonomic origin of these nerve fibers and have been shown to regulate blood flow, like calcitonin gene-related peptide and substance P.

Chemical substances released from cells and vessels after damage by noxious stimuli activate nociceptive afferent endings and generate action potentials conducted to the CNS. A lot of factors and mediators can further influence the process of excitability in the nociceptive endings [21]. Like in inflammation, damage of peripheral tissues can result in release of substances from blood vessels, from cells of the immune system or from nerves themselves (neurotransmitters like glutamate, neuropeptides, neurotrophins, products such as norepinephrine from sympathetic efferents). Increased excitability of nociceptors at the site of injury is termed peripheral sensitization. Damage can sometimes also lead to phenomena such as nerve sprouting or abnormal nerve changes with the result of ectopic or aberrant neural discharges which beside others are involved in neuropathic pain conditions [19]. In view of nociceptive afferents, peripheral sensitization is clinically expressed in a decreased activation threshold (allodynia – pain produced by a stimulus which is normally non-noxious), increased suprathreshold responsiveness (hyperalgesia – increased sensitivity to noxious stimuli), spontaneous activity (spontaneous pain) and involvement of adjacent afferent nerve endings (pain spread). By increased nociceptor activity, functional changes in central nociceptive processing are induced which lead to central sensitization and contribute to secondary hyperalgesia (elevated pain sensitivity beyond the site of tissue injury), expansion of neuronal cutaneous and/or deep receptive fields or – in some cases – to persistent pain.

TMJ pain mentioned by the patient and clinically evaluated by lateral or posterior joint palpation is frequently thought to be associated with an inflammation

of the joint. However, this assumption is not always correct because painful joint palpation and perception, respectively, can be present not only due to peripheral sensitization on the basis of a local problem in the joint – or adjacent jaw muscles – but also due to central sensitization or dysregulation, which may contribute to spontaneous pain and pain spread or referral [22] (see also the chapter by Kopp and Sommer, pp 28–43). Due to the close topographic neighborhood of the deep portion of the masseter muscle to the joint, the additional question arises about the validity and reliability of lateral joint palpation. Furthermore, the induction of peripheral and central sensitization does not only depend on inflammation. The cytosolic release of glutamate (which does not appear to produce any substantive inflammatory reactions) from affected neurons as well as nonneuronal cells, such as macrophages, blood serum or Schwann cells, can play a role in modulating the sensitivity of deep craniofacial tissues through autocrine and/or paracrine-regulated glutamate receptor mechanisms [23].

Arthralgia is further involved in distinct phases of nonspecific joint disease, i.e. osteoarthritis (OA), and of other specific joint diseases, such as rheumatoid arthritis. In general, OA is primarily characterized by cartilage degeneration [24]. The breakdown of major matrix macromolecules, such as collagen and proteoglycan, is triggered by enzymatic activity in which matrix metalloproteinases play an important role (fig. 2).

Increased amounts of matrix fragments are detectable in the synovial fluid and may produce a variable degree of synovial inflammation. The inflammation of the synovial membrane creates mediators including interleukin 1β and tumor necrosis factor α which play a pivotal role in further cartilage destruction and the inflammatory process.

Rheumatoid arthritis is a chronic inflammatory connective tissue disease of systemic character [26] and primarily affects periarticular structures, especially the synovial membrane. The disease process starts as an inflammatory reaction transforming the synovial membrane into hyperplastic and granulomatous tissue by release of cytokines, among them interleukin 1β and tumor necrosis factor α. It becomes more and more evident that the inflammatory mediators (cytokines, growth factors, enzymes) of synovial tissue in osteoarthritic joints are similar to the inflammatory mediators found in joints afflicted by rheumatoid arthritis. Differences are mainly quantitative, showing lower values in OA [27]. Although absolute levels of particular mediators may be indicative of their role, the final effect on joint tissues is determined by the balance of synergizing, counteracting and regulating mediators. An unfavorable balance between destructive proteases and protease inhibitors is found in OA as well as in rheumatoid arthritis. Levels of interleukin 1β, tumor necrosis factor α, serotonin and prostaglandin E_2 in TMJ synovial fluid are associated with TMJ pain and allodynia/hyperalgesia. Since none of these mediators seem to be

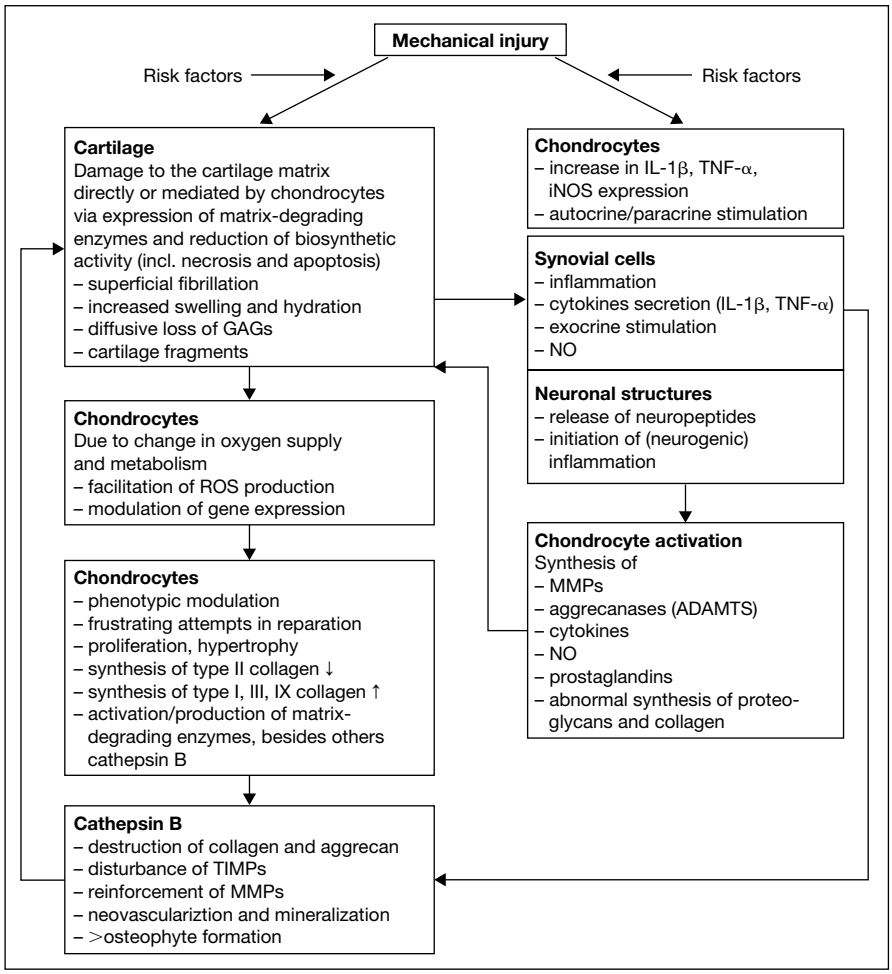

Fig. 2. Supposed pathophysiological mechanisms in OA/osteoarthrosis (modified after Palla [16] and Baici et al. [25]). Left column: cytokine-independent events (likely nonpainful in clinical presentation); right column: cytokine-dependent events (dominate in painful episodes). Both event chains may coexist. ADAMTS = 'A disintegrin and metalloproteinase with thrombospondin motifs'; GAGs = glycosaminoglycans; iNOS = inducible nitric oxide synthases; IL = interleukin; MMPs = matrix metalloproteinases; NO = nitric oxide; ROS = reactive oxygen species; TIMPs = tissue inhibitors of metalloproteinases; TNF = tumor necrosis factor.

detectable in the synovial fluid of healthy individuals, they might become useful for diagnostic purposes and therapeutic targets [28, 29].

Little is known about (specific) risk factors for TMJ arthralgia. It seems to be that jaw clenching, third molar removal and somatization show a certain

association with arthralgia, whereas in myofascial or combined pain groups trauma, clenching, third molar removal, somatization and female gender are significantly associated [30]. The role of trauma is also well recognized. It is one of the risk factors in nonspecific painful arthogenous conditions. Individuals with a history of extrinsic trauma had risks of precipitating TMJ pain and limited jaw opening that were 2.14 and 2.85 times greater, respectively, than in persons without trauma [31]. It was also concluded from this 4-year longitudinal study that these symptoms usually resolve [31]. Furthermore, studies suggest that subjects with muscular diagnoses have more pain and psychological distress than those with joint diagnoses [32, 33]. A number of factors is under discussion for an individual's susceptibility for TMJ OA: age (reduced adaptation capacity in higher age), female predisposition (estrogen and the receptors), genetic background (e.g. polymorphism of the catechol-O-methyltransferase gene), dietary intake (generation of prostanoids, isoprostanes and leukotrienes from fatty acids with proinflammatory and pronociceptive effects; anti-inflammatory effects of derivates of omega–3 fatty acids; antioxidant capacity of vitamins E and C; possible protective effects by dietary supplementation with glucosamine or chondroitin sulfate) [34, 35].

Diagnosis

Besides congenital disorders and neoplasms, the American Academy of Orofacial Pain classification of nonspecific painful TMJ conditions includes disk displacements with and without reduction (acute and chronic), hypermobility and dislocation, inflammatory conditions, OA (primary and secondary), TMJ ankylosis, adhesion and fracture. A disharmony between load and load tolerance may explain the occurrence of signs and symptoms of painful TMJ conditions in some patients and not in other individuals. None of the supposed risk factors is indicative or can predict any of the TMD subgroups and nonpatients. Signs and symptoms (by classification criteria) give clues to a clinician as to the condition involved. In this respect, researchers and clinicians need to realize that the patient population with acute and subacute painful TMJ conditions is different from the referred population with mostly chronic complaints seen in specialized clinics. Most of the scientific body of knowledge does not target the conditions seen in daily practice. This fact has consequences for both the clinician and researcher. It is important to realize that the choice of diagnostic techniques and management strategies also depends on this distinction. The general rule in diagnostic tests is to increase the pretest probability of the condition in a certain population. In positive predictive values of tests, the prevalence of the disease in the population is reflected. The clinician must know

the relation of such a value and the population under study. In conclusion, clinicians in TMD centers with referred patient populations will use other diagnostic strategies than single first-line clinicians. Research findings on diagnosis (sensitivity, specificity, positive and negative predictive values) in general do not apply to populations in general dental practice.

In the clinical diagnosis of arthralgia, pain referral from the throat and the side of the tongue to the area of the TMJ and the ear always needs attention (fig. 1, non-TMDs). These pains can be the first indicator of neoplastic changes; consequently, there is a necessity of rapid referral to avoid delay. The odds to be confronted with these patients in first-line care is much lower than in specialized clinics. This is another example of the differences in diagnostic reasoning as indicated in figure 1. In general practice, pain with a dental origin and referred pain patterns in the side of the face should always be considered and excluded first.

Clinical Diagnostic Tests

Clinical tests need to render reliable results, while realizing that the signs and symptoms may contain noise besides signal. The minimal change of signs and symptoms defined by test-retest characteristics is a clinically very relevant parameter in the follow-up of both patients and of management strategies. This variability may also be the result of a lack of diagnostic standards and may be influenced by several therapist- and patient-related aspects. It is important to recognize that large observer variation is not restricted to the clinical registration of signs and symptoms of musculoskeletal disorders. Large variations occur also in the recording of cardiovascular signs, gastrointestinal signs and respiratory signs [36, 37]. In a clinical setting, we must accept a certain amount of variation in signs and symptoms, and for this reason, it is important not to base a diagnosis on the results of a single test. The reproducibility of signs and symptoms needs always to be taken into account, while the patient history, clinical examination, and test results must point to the same direction to arrive at a proper working diagnosis.

Multitest scores (MTSs) [38, 39] are combinations of several related variables. An MTS is considered positive when a sign is brought on by one or more parts of an orthopedic test. Pain can be provoked by active mandibular opening only, or on excursive movements. In both situations, the MTS ‘pain in active movements’ is scored positive (table 1). Two examiners may agree on myofascial pain but disagree on the muscle(s) involved. Table 1 offers our results regarding interexamination reliability of MTSs for combinations of tests as to the cardinal symptoms of TMD: pain, restriction of motion and joint noises. It

Table 1. Interexaminer reliability of the MTSs for combinations of tests for the 3 main symptoms of TMDs

MTS categories	Agreement, %	κ	Presence of signs and symptoms, %
Pain			
During active movements	65	0.3	49
During additional tests (passive opening, joint play, compression static pain)	69	0.4	59
During function (active movements and/or additional tests)	89	0.7	69
During function and palpation	96	0.8	91
Noises			
During active movements	80	0.6	55
During additional tests	68	0.3	32
During function	77	0.5	60
Restriction of movement			
During active movements	92	0.6	10
During active movements and/or joint play tests	75	0.4	29

κ: Cohen's kappa statistic in a TMD patient group (n = 79).

is obvious that the reliability of an MTS cannot be better than the least reliable test being part of the MTS. From a clinical viewpoint subgroup classifications are the ultimate MTSs. For clinical diagnostic purposes and treatment decisions MTSs provide sufficient information. The kappa statistic evaluates the proportion of agreement between examiners in relation to the proportion expected by chance alone. It is known that κ-values become unstable when there is a large proportion of agreement, and most of the agreement is limited to only one of the possible rating choices. This problem has been described as 'limited variation' [38]. Whenever the prevalence of positive findings lies between 0–10 and 85–100%, limited variation should be suspected.

Clinicians will never use only a single test in the total diagnostic process of a (nonspecific) TMD condition, which otherwise supports the use of MTSs in reliability studies. For example, disk displacement with reduction is clinically recognized by the combination of the following 5 cardinal criteria [5–7, 41]: reciprocal TMJ clicking, elimination of reciprocal clicking on jaw opening and closing on protrusion, reproducible clicking during opening, protrusion and

contralateral excursion, clicking on opening louder than on closing, resistance on closing produces a louder click than without resistance. The more of these clinical criteria are fulfilled, the higher are the chances to predict the presence of an anterior disk displacement with reduction correctly by clinical means only. However, there is no clear-cut criterion (e.g. 3 out of 5 positive findings) for its presence or absence. In the same way the sudden change of clicking, pain and (periodic) locking into locking and pain only is clinically indicative for a disk displacement without reduction. Additional findings, such as limitation of mandibular movement towards the opposite side and in protrusion, as well as deviation to the affected side and on protrusion, are good indicators to enhance prediction. For these painful arthrogenous conditions, mandibular traction and translation may offer extra information. In myogenous limited jaw opening, it is striking that lateral excursions and protrusion are not restricted, and passive opening beyond the active range does result in greater jaw opening (up to 10–15 mm) at the cost of pain in the masticatory muscles, mostly the masseter. General dental practitioners usually expect certainty, rather than to have learned to cope with less than 100% certainty. With respect to painful TMJ conditions, oral surgeons know through arthroscopy that the TMJ shows much more abnormalities than can clinically be evaluated. In cooperation with biomedical researchers, it is within their competence to select those characteristics that add to the existing clinical characteristics to better diagnose and treat or manage these conditions.

Recognizing the above-mentioned considerations, a broad consensus exists as to the need of a comprehensive clinical examination being the first approach to be able to arrive at a working diagnosis, problem list and management program. The history (both by oral history-taking and using a questionnaire) addresses pain characteristics, TMJ signs and symptoms proper, impact on daily activities in general and oral function in particular, correlates, general health and psychosocial factors. The comprehensive physical examination consists of intra- and extraoral inspection and orthopedic testing (active movements, passive opening and palpation of the masseter and temporalis muscles, and per indication compression and traction and translation tests). The combination of comprehensive history-taking and physical examination of the referred population shows a proper prediction of subgroups, e.g. the discrimination between arthrogenous and myogenous TMD subgroups (table 2) [42]. We advise using the following orthopedic tests with an adequate reliability (κ-values > 0.4): active movements, passive opening, palpation of the muscles that can be palpated (masseter and temporalis muscle, temporalis tendon). Compression, and traction and translation can be performed when still in doubt or on indication: testing for hypermobility and in presumed painful TMJ conditions when one is not relying on palpation or other pain tests. Our studies

Table 2. Percentage of subjects correctly classified (% corr.) by the different tests and combination of tests selected by stepwise logistic regression and odds ratio (OR) of the myogenous group M (n = 69) versus the arthrogenous group A (n = 91)

	Class.	M	A	OR
Active movements	78.6	84	74	15.36
Palpation	70.0	45	90	7.65
Combination of active movements and palpation	83.1	87	80	26.75
Passive opening	73.4	54	89	9.16
Joint play test	66.5	80	56	5.11
Compression	58.4	9	97	3.18
Static pain test	71.8	45	92	8.77
Combination of 4 additional tests	77.3	65	86	11.68
Combination of 6 tests	87.5	87	88	48.49

Class. = Total percentage of correctly classified patients.

indicate that the cardinal clinical symptoms – pain, restriction of movement and joint sounds – can be established reliably using the concept of MTSs (table 1).

Imaging

The imaging technique of first choice for arthrogenous TMJ conditions is the panoramic radiograph. Both from a standpoint of radiation dose and clinical utility, this technique – together with the patient history and clinical examination – is able to help the clinician to rule out disorders of the teeth, the periodontium, the jaws and the sinuses. It also gives a good impression of the mandibular condyles and allows for left/right comparison. The role of additional imaging is limited. Clinical and radiological findings generally do not mutually match. More sophisticated imaging techniques such as magnetic resonance imaging (MRI) or computerized tomography (CT) are mandatory in those cases where the symptoms cannot be explained sufficiently or are refractory to adequate management (quality, compliance) and in any case when a specific painful TMD condition is suspected such as developing asymmetries, change of the occlusion (e.g. vertical open bites), trauma and neoplasia [43, 44]. CT scans or MRI (with or without extrinsic contrast such as gadolinium) have proved to give additional diagnostic information regarding affected tissues such as cartilage and bone, or in the evaluation of synovial tissue and the presence of effusion (MRI). T_2-weighted MRI images always assist in ruling out

inflammatory conditions with the subsequent effect on therapeutic decisions. In suspected condylar growth disorders, scintigraphy can show high metabolic activity (hot spot). In earlier years, disk position was the target of additional imaging techniques, such as arthrography, CT and MRI. Due to a better insight into the variation of disk position in patients and nonpatients, the indication for additional imaging has shifted to depict the status of the fibrous cartilage layer covering the TMJ surfaces and inflammatory related effusion. In this respect, a poor agreement was found between clinical TMJ pain and TMJ effusion in a sample of unilateral TMJ pain; TMJ MRI findings characteristic for OA were significantly correlated with clinical TMJ pain. TMJ pain as such seems a poor predictor for MRI-based inflammatory TMJ conditions [45].

Diagnostic Injections

The dentist is well educated to use diagnostic injections intraorally (e.g. in the verification of dental pain). The diagnostic elimination by anesthetic injection of extraoral pain sources (myogenous or arthrogenous), not sufficiently diagnosed by other clinical means, is less often used by dentists. Sometimes, therapeutic effects are encountered, e.g. when prolonged relief of pain may interrupt pain cycling [12]. Diagnostic anesthetic blocks are described intra-articularly [9] and extra-articularly (auriculotemporal nerve) [12]. The use of the proper substance depends on the tissues involved, the presence and degree of inflammation and the desired short- or long-term effects. The scientific literature on injection therapy is scant with respect to the orofacial area in general, and the TMJ area in particular. Conversely, clinical experience is very positive about this powerful tool that is used too sparsely.

Management and Prognosis

In the case of specific TMDs, the treatment should be as specific as possible. Examples are surgical procedures in growth disturbances and neoplasia, and medical treatment (medication) or in combination with occlusal appliances in systemic disease (e.g. rheumatological). In nonspecific TMDs, the management options may vary according to the diagnostic subgroup involved. The results of intervention studies do not yet support the hypothesis that individualized treatment based on subgroup classification will lead to higher success percentages (e.g. occlusal splints, physiotherapy, patient education). Management options need to be tailored to axis I (physical conditions), axis II (psychosocial status) and axis III (prognosis). Axis III, which is not part of the RDC/TMD,

describes additional clinical consideration regarding prognosis, such as chronicity, the result of earlier interventions, comorbidity, the relative components of nociceptive and/or neuropathic characteristics of pain, the course of the condition and medication (fig. 1). Although not defined as axis III before, the encompassed aspects are at least equally important as axes I and II with regard to prognosis and treatment plan.

Apart from the stability of signs and symptoms already discussed above, the clinician has always to deal with yet other sources of variation. In patients presenting with pain and limited mandibular movement, the regression to the mean effect is the most common source [46].

To define clinically relevant changes, the smallest detectable change needs to be exceeded [47]. In jaw opening, this has been found to be 5 mm in healthy individuals and 9–6 mm in painful restricted TMJ function (single vs. repeated measurements). In pain studies, a change of 43–15 mm on a visual analogue scale and 22.7–14.4 units on a pain rating scale (McGill Pain Questionnaire, Dutch language version) has been described (single vs. repeated measurements) [47]. The Mandibular Function Impairment Questionnaire describes mandibular function, such as chewing, laughing, yawning and speech; a change of 14–10 units on this scale is beyond biological variation.

Although not often addressed in the literature, the prognosis of nonspecific therapy is important in patient communication and management. Fricton et al. [48] described complex and simple cases on the basis of problem lists in order to allocate various therapeutic regimes. Complex patients were offered a team approach consisting of splints, physiotherapy and psychological treatment. Fricton and Olsen [49] concluded that pretreatment psychosocial information is important in predicting therapeutic outcome for chronic TMDs. Symptoms of depression mediate therapeutic response in patients with chronic pain. De Leeuw et al. [50–52] described the role of psychosocial factors and TMDs: its relation to treatment-seeking regarding TMDs, subgroups of TMD and their influence on therapeutic outcome. To that end, individuals recruited by primary care dentists and consulting them for dental problems and consecutive patients referred to the department of TMD/orofacial pain (OFP) were requested to fill in a comprehensive anamnestic questionnaire. The patients (clinical cases) were clinically examined and they completed an extra set of questionnaires [50–52]. The dental patients were subdivided into those without any TMD signs and symptoms (community controls) and those having signs and symptoms (community cases). Clinical cases were classified as having arthrogenous, myogenous or combined arthrogenous/myogenous symptoms. The subjective need for TMD management can be determined by the number and severity of TMD symptoms, while being mediated by health locus of control and coping style. Psychological factors such as self-efficacy and locus of control play a role in

the adaptation to chronic illness. Self-efficacy is a behavior-specific characteristic which can be altered by education programs. Health locus of control is the extent of an individual's perceived control over health outcomes. Dysfunctional coping strategies are characterized by a passive attitude, exaggeration of negative consequences (catastrophizing) and a limited use of distraction strategies, associated with greater levels of distress. Conversely, individuals with high internal locus of control are more likely to take control of their own health condition. The assessment of psychosocial factors, in particular health locus of control, is important for understanding the subjective treatment need and therapeutic outcome. Clinical cases more frequently considered health to be determined by chance or fate than community controls and community cases. Analysis of the symptom profiles of patients and controls using the comprehensive questionnaire showed that patients with a mainly arthrogenous condition can be distinguished by fewer parafunctions, ear symptoms and fewer TMD correlates, such as pain in the head, neck and shoulder. TMD patients with a mainly arthrogenous condition had fewer general health symptoms. A replication study in an independent sample of clinical cases verified most of these findings [32]. Therapeutic efficacy may be enhanced if clinicians were able to select patients who are unlikely to respond to therapy. Health locus of control and coping style were found to be good indicators [52]. This underlines the need to assess these factors in clinical care. Providing patients with comprehensive information about the mechanisms underlying their complaints along with conventional management improves therapeutic outcome. Patients with a negative therapeutic outcome were also characterized by more general health symptoms, a higher number of symptoms and correlates of TMDs, more jaw symptoms, more ear symptoms and more painful or sensitive areas in the head, neck and/or shoulders [52].

In TMJ osteoarthrosis, the long-term evaluation of patients with a history of OA in the TMJs has clearly indicated that patients after 30 years do as well as individuals not afflicted by the disorder regarding mandibular function, for example with regard to chewing, oral habits and general joint osteoarthrosis [53]. Clinicians can use this information to reassure patients with negative beliefs based on the worse prognosis of osteoarthrosis of other joints (e.g. the hip).

Systematic reviews are regarded in the highest ranks of scientific evidence. Although not at debate as such, evidence-based care by a clinician is not limited to the results of such reviews, but also embraces the clinical experience of the clinician and patient preferences. In the field of TMDs and OFP, this provides the clinician with an abundance of combinations of therapeutic modalities that can be used to deliver adequate care to patients. Key elements for success are partnership, the translation of the evidence for modalities to be used and not to be used, in understandable words, investing time in communication and addressing

the questions of patients. The choice of disciplines to be joined in a team around the patient is driven by factors such as the type of the disorder (specific disorder with anatomical and physiological variables), related psychosocial issues (patient personality and the context) and prognostic factors, such as the acuity (acute, chronic) and complexity (earlier treatments without success and relapse, comorbidity, surpassing normal healing time; fig. 1). For these reasons, reviews on therapeutic effects have practical limitations that should be considered as well. In offering treatment, the clinician also needs to know if the research population is representative for the patient and if not how much this will hamper translating the results of the review to his or her individual patient.

Recently, a systematic review regarded occlusal splints and occlusal adjustment in myogenous and arthogenous TMD patients [54], based on a former review [55]. Moreover the critical comments provided a broad perspective as to the original message [56–58]. Other recent systematic reviews only included myogenous TMD and were excluded from this chapter [59, 60]. Of the originally reviewed 20 studies, 11 included arthrogenous TMD (table 3) [52]. Of the 11 studies on arthrogenous conditions, 7 were on occlusal splints and 4 on occlusal adjustment [52]. Some were on combined arthrogenous/myogenous groups, the latter being more realistic in clinical practice, since the pure arthrogenous and myogenous cases are rare. The efficacy of treatments gets only value when they are compared with another active or passive treatment or placebo. Effect sizes were not provided, but the comparison of the various treatment modalities is informative as to efficacy (table 3). Apart from the critical comments mentioned above [56–58], such as variation in instructions on wearing splints, recruitment of patients or use of hard acrylic and soft splints, other remarks were made, which shed a more optimistic light than the conclusion from the original review [58]. There is no doubt about the necessity of better research, with more patients and more similar instructions. However, the enormous amount of patients that need to be examined in clinics to be included in such studies raises doubt as to the generalizability of the study. Multicenter studies, such as those carried out by the RDC/TMD initiative, can partly cope with this problem. The more calibration takes place in such studies, the less the results are generalizable to other clinical populations, e.g. first-line clinicians. The more results from randomized clinical trials are available, the more we will find similar treatment results in these nonspecific TMDs. In myogenous TMDs, it is striking that regardless of the therapeutic regimen (occlusal adjustment, occlusal splint, physiotherapy, counseling) 60–70% positive treatment results are achieved [75, 76] It is tempting to speculate about the same results in nonspecific arthrogenous TMD conditions. Thinking in this line, the question arises how many trials need to be done before realizing that this will not help offering a better therapy to our patients.

Table 3. Details of randomized controlled trials on the use of occlusal splints and occlusal adjustment for treatment of nonspecific arthrogenous temporomandibular conditions

Diagnostic groups	Study	Therapies	Outcome measures	Follow-up	Score	Efficacy
Occlusal splints						
A/M: mandibular dysfunction (n = 15)	Dahlström [61], 1982	Stabilization splint at night for 6 weeks	Subjective rating of symptoms;	4 weeks	0.32	>BL
		Biofeedback 5.3 × 30 min	Helkimo Clinical Index			= control treatment
A: pain and dysfunction of the masticatory system + reciprocal clicking (n = 23–24)	Lundh et al. [62], 1985	Stabilization splint at night for 6 + 2 weeks	Reciprocal clicking; tenderness to muscle	6 weeks	0.39	= control treatment
		Anterior repositioning splint, 24 h for 6+2 weeks	palpation	7 weeks		= passive control
		Control group		52 weeks		
A: pain and dysfunction of the masticatory system + disk displacement (n = 20–22)	Lundh et al. [63], 1988	Stabilization splint at night for 6 months	Pain VAS; clicking; tenderness to	6 months	0.44	= control treatment
		Occlusal onlays	palpation			(<control treatment regarding clinical signs)
		Control group				= passive control

A/M: craniomandibular disorder (n = 30–40)	List et al. [64], 1992 List and Helkimo [65], 1992	Stabilization splint, acupuncture Acupuncture 6–8 × 30 min Waiting list control	Pain VAS; subjective improvement; Helkimo Anamnestic Index; Helkimo Clinical Index; activity of daily living	6–8 weeks 6 months 12 months	0.47	>BL = control treatment >passive control
A: TMJ disk displacement without reduction (n = 25–26)	Lundh et al. [66], 1992	Stabilization splint at night for 12 months Control group	Overall treatment results; 79 clinical variables	12 months	0.24	= passive control
A: TMJ disk displacement without reduction (n = 15–16)	Linde et al. [67], 1995	Stabilization splint, 24 h for 6 weeks TENS, 6 × 15 min	Positive responders; frequency of complaints; severity of complaints; symptom questionnaire; pain registration	6 weeks	0.44	= control treatment

Table 3. (continued)

Diagnostic groups	Study	Therapies	Outcome measures	Follow-up	Score	Efficacy
A: TMDs of arthrogenous disorders (n = 30)	Ekberg [68], 1998	Stabilization splint, at night for 10 weeks Palatal splint, at night for 10 weeks	Pain VAS; verbal pain rating; frequency of pain; overall change in subjective symptoms; tenderness to palpation of TMJ; Helkimo Clinical Dysfunction Index	10 weeks	0.71	>BL >control treatment
Occlusal adjustment						
A: TMJ pain and dysfunction (n = 20)	Werndahl et al. [69], 1971	Occlusal adjustment Muscle exercise	Subjective improvement	6 weeks	0.24	= control treatment

A/M: mandibular dysfunction (n = 15)	Wenneberg et al. [70], 1988	Occlusal adjustment Different stomatognathic treatment methods	Subjective dysfunction score Clinical dysfunction score	2 months	0.40	>BL <control treatment
A/M: craniomandibular disorder (n = 25)	Vallon et al. [71], 1991 Vallon et al. [72], 1995	Occlusal adjustment Control group	Pain VAS; overall changes in severity; clinical signs	1 month 3 months	0.57	>BL = passive control
A/M: craniomandibular disorder (n = 23–28)	Tsolka et al. [73], 1992	Occlusal adjustment; mock Mock occlusal adjustment	Prevalence of symptoms; Helkimo Anamnestic Index; Helkimo Clinical Index	10 days	0.36	= control treatment (placebo)

Modified from Forssell and Kalso [54]. Score: reviewers' score based on quality scale of Antczak et al. [74]. Efficacy: reviewers' overall conclusion of efficacy when emphasis was put on results at the longest follow-up of each study; > = results significantly better than; = = results comparable to; < = results significantly worse than. A = Arthrogenous; BL = baseline; control treatment = any active control treatment; M = myogenous; passive control = control group without any treatment or waiting list control; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.

Different from the focus in the literature, the general dental practitioner will be confronted much more frequently with acute simple cases that have a better prognosis than chronic complex cases. The role of the clinician is mainly to guide the patient with pain and impaired function through this period, reduce the level of distress and avoid harm by rigorous treatments proposed by other treatment providers. This can be fulfilled by education, medication, achievement of orthopedic stability and rehabilitation strategies (see paragraph about physiotherapy). The role of the first-line clinician is to avoid chronicity by reducing pain by appropriate intervention.

The role of occlusion in the etiology of TMD in general and in painful TMJ conditions specifically is not well understood yet. Based on a systematic Cochrane review of 6 trials that included 392 mostly healthy subjects or those with only minor TMD signs and symptoms, the authors concluded that there is an absence of evidence that occlusal adjustment treats or prevents TMD [77]. However, since there is a supposed minor etiological occlusion-related component, which has never been rejected, occlusal adjustment cannot be discarded. The authors of this chapter realize that discussing occlusion with regard to painful TMJ conditions is not recognizing its broader meaning in prosthetic dentistry. The clinician always needs to answer the question whether the occlusion is changed or different from a clinical reference position (e.g. retruded contact position) due to a structural (TMJ or other) reason. In such a case the occlusal characteristics are the result of an arthrogenous condition, rather than the other way around. Therefore, preference for the use of reversible instead of irreversible treatment strategies (occlusal splints) is generally accepted. This relates especially to adjustment of the intercuspal position to postulated ideal occlusal characteristics. If migration of teeth is hampering the mandible to reach the intercuspal position, correction can be part of the treatment plan. The occlusal splint is supposed to offer orthopedic stability to the masticatory system. Repositioning of the TMJ disk to its 'original' position is no longer a treatment goal.

The use of medication has been tested in a randomized controlled trial, contrasting diclofenac (Voltaren, 50 mg 3 × per day in the 1st week, twice a day in the 2nd week) with placebo in nonspecific painful TMJ conditions (n = 32) [78]. There was a significant reduction of daily TMJ pain in the diclofenac group. The same drug was tested contrasting no treatment and palliative treatment, 25 mg 3 × per day for 2 months in painful anterior disk displacement without reduction, confirmed by MRI (n = 69) [79]. The authors concluded that all groups showed improvement of their signs and symptoms with time. The positive outcome was attributed to the passage of time, rather than to a specific type of treatment effect.

The combination of nonsteroidal anti-inflammatory drugs (ampiroxicam, 27 mg once a day) and physiotherapy (mainly active and passive movements,

among others stretch) in a homework program was contrasted with no treatment in a 2- to 4-week randomized controlled trial [80]. There was a 60% improvement in the treatment group (n = 30) in contrast to the controls (n = 30, 30% improvement). The number needed to treat was 3.75 (95% confidence interval 2.1–65.9). This therapeutic combination was found to be effective as a primary treatment of patients with painful disk displacement without reduction and without osseous changes.

Physiotherapy

In the field of TMDs and OFP, physiotherapy became a more frequent treatment option in the last decades. A well-documented and often cited review regarding physiotherapy and OFP was published by Feine and Lund [81]. In 2006, two systematic reviews regarding physiotherapy and TMDs added to the existing knowledge [82, 83]. However, only few of the reviewed studies involved painful arthrogenous conditions.

The World Organization for Physiotherapists describes physiotherapy as a health profession concerned with the assessment, diagnosis and treatment of disease and disability through physical means [84]. Physiotherapy is based on principles of medical sciences, and it is generally held to be within the sphere of conventional medicine. It uses physical approaches to promote, maintain and restore physical, psychological and social well-being. The major conditions managed by physiotherapists can be broadly grouped into 3 categories: musculoskeletal, cardiopulmonary and neurological. OFP and TMDs are part of the greater musculoskeletal field where physiotherapists bring in their clinical judgement. Physiotherapy applications for TMDs and OFP include a wide variety of techniques and therapeutic modalities that have been commonly used to alleviate pain, reverse the dysfunction and restore optimal muscle and joint function, including posture as well as disabilities related to activities of daily life. Rehabilitation management is based on all aspects of human health and some health-relevant aspects of well-being. The International Classification of Functioning, Disability and Health [85] provides a structure to present this information in a meaningful, interrelated and easily accessible way in two parts (part 1 – functioning and disability: body function and structures, activities and participation; part 2 – contextual factors consisting of environmental factors and personal factors). The use of this classification, which is a biopsychosocial model, has been described by Steiner et al. [86]. It may also serve chronic TMD rehabilitation.

The physiotherapeutic approach should be tailored to the individual patient. It often includes a homework program with different exercises, instructions for

automassage, habit reversal techniques, relaxation, next to general information as well as ergonomic and other lifestyle advice [75, 87, 88]. Like other health care providers, physiotherapists should take extra time to inform and educate patients. Patients require adequate information to assist them in making choices and overcoming unhelpful beliefs and, when necessary, help them in modifying their behavior. In this respect, physiotherapists are better trained than general dental practitioners. The role of education in painful TMJ conditions is not clear. Despite this lack of evidence, patient education is always part of the management.

No studies are available on physiotherapy in acute or subacute TMJ conditions. In chronic painful TMJ conditions, trials show a positive trend to implement exercises in the treatment plan [89–91]. Due to a lack of high-quality studies, the results for physical therapy modalities and massage therapy are still inconclusive. For manual therapy, there are clinically relevant results for spinal, shoulder and hip disorders.

The Cochrane reviews on transcutaneous electrical nerve stimulation for chronic pain [92] and low-level laser therapy on OA in other joints than the TMJ [93] show a lack of evidence regarding effectiveness. Using the combination of low-level laser therapy and exercises, clinically relevant effects were found in active and passive maximum mandibular opening, excursive movements and the number of tender points in TMD patients with an arthrogenous and myogenous component [94]. No significant differences were found regarding pain reduction. Since the treatments were used in combination, the effect of either therapy cannot be revealed. The effect of exercises will probably prevail over laser therapy effects. The location-specific dosage may hamper the correct evaluation of laser effectiveness [95]. They proposed doses for various joints, including the TMJs. The included studies on TMJ pain used dosages within the prescribed limits. However, testing and calibration of laser output was only performed in 2 of the clinical trials (out of 11 trials, 565 patients). Clinically relevant effects of low-level laser therapy regarding pain reduction using a visual analogue scale in the knee, zygapophyseal joint and TMJ were found, the visual analogue scale weighted mean differences being 30 mm (95% confidence interval 19–41). Cautious interpretation is still needed, however, since the studies on low-level laser therapy also showed some methodological weakness, large variation in treatment procedures, no control of cointerventions and only short-term evaluation.

Based on information from the meta-analyses and Cochrane reviews, the overall conclusion is that the evidence of efficacy of physiotherapy is especially proven for exercise therapy. This refers to all domains, musculoskeletal, neurological and cardiopulmonary. Carmeli et al. [89] studied manual mobilization and active excursions of the mandible in the treatment of temporomandibular

pain and limited range of motion. The authors compared the effect of a physiotherapy program with the use of a soft repositioning splint in participants with an anterior displaced disk with unstable reduction in excursive movements. Overall, this study was considered methodologically weak by the reviewers [82] (Jadad score: 1 of 5 [96]).

The authors concluded that the use of exercise therapy in the arthrogenous type of TMD patients was more effective in order to increase jaw opening and decrease the pain than the soft repositioning splint. In clinical practice, traction and translation techniques, postisometric relaxation and the exercises as discussed by Carmeli et al. [89] are frequently used and rated positively. Exercises described by Yoda et al. [90] and Minagi et al. [91] can be introduced to patients with anterior disk displacement with and without reduction, respectively. In summary, these results support the use of such programs and urge the need for further research. Treatments are not equally effective across the whole spectrum of patients with chronic TMDs. The combination of these therapies with biomedical approaches also needs further attention. The content of an example of such a home physical therapy exercise program for nonspecific myogenous TMDs was published by Michelotti et al. [88].

In conclusion, the approach for acute TMD conditions with a normal course will be counseling, including general information, and, if indicated, a tailored exercise program depending on the type of the disorder and the specific conditions related to the International Classification of Functioning, Disability and Health domains: body structures, function, activities and participation. When there is a deviant course in an acute and subacute condition, it is essential to avoid chronicity; effort must be placed on influencing the risk factors, including pain intensity, depression, anxiety and self-esteem. For the chronic conditions with a deviant course (inadequate handling, hardly any self-discipline, no adequate coping, no fine tuning of load and load tolerance, decreased participation), the exercises must be behavior oriented. TMDs show much more similarities than differences to other chronic pain conditions. Health care providers need to realize this notion and use the knowledge gained from the broad domain of chronic pain research.

Conclusion

In nonspecific painful TMJ conditions, percentages of positive therapeutic results vary minimally regardless of the treatment regimen. This may indicate that nonspecific painful TMJ conditions can be managed with various nonspecific treatment procedures. Especially in acute and subacute conditions, the general (dental) practitioner can offer adequate patient education, pain medication,

as well as orthopedic stability to the masticatory system (reversible occlusal splints and adequate physiotherapy). To enforce compliance, the clinician is advised to introduce modalities close to the preferences of the patient. Management is aiming at reducing signs and symptoms to a level that the patient can cope with. A proper working diagnosis appears to be the key issue rather than the specific treatment effects of these modalities. Combinations of therapeutic measures seem to do better than single modalities. Comorbidity will modify and mediate the therapeutic approach.

References

1 Okeson JP (ed): Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management, ed 3. Chicago, Quintessence, 1996.
2 Merskey H, Bogduk N (eds): Classification of Chronic Pain, ed 2. Seattle, IASP Press, 1994.
3 International Classification of Headache Disorders, ed 2. Cephalalgia 2004;24(suppl 1):1–160; revised Cephalalgia 2005;25:460–465.
4 McNeill C (ed): Temporomandibular Disorders: Guidelines for Classification, Assessment, and Management, ed 2. Chicago, Quintessence, 1993.
5 Dworkin SF, LeResche L: Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord Facial Oral Pain 1992;6: 301–355.
6 Lobbezoo-Scholte AM: Diagnostic Subgroups of Craniomandibular Disorders; thesis, Utrecht University, 1993.
7 Lobbezoo-Scholte AM, de Leeuw JRJ, Steenks MH, Bosman F, Buchner R, Olthoff LW: Diagnostic subgroups of craniomandibular disorders. I. Self-report data and clinical findings. J Orofac Pain 1995;9:24–36.
8 Steenks MH: Including, excluding or diagnosing: guest editorial J Orofac Pain 2004;18:81.
9 Stegenga B: Osteoarthritis of the temporomandibular joint organ and its relationship to disc displacement. J Orofac Pain 2001;15:193–205.
10 Steenks MH: Specifieke en aspecifieke temporomandibulaire dysfunctie: gastredactioneel. Ned Tijdschr Tandheelkd 2005;112:44–45.
11 Projectgroep musculoskelettale stoornissen van het kauwstelsel: Musculoskelettale stoornissen van het kauwstelsel. Consensus diagnostiek en therapie in de gnathologie. Ned Tijdschr Tandheelkd 2003;110:281–287.
12 Okeson JP: Bell's Orofacial Pains, ed 6. Chicago, Quintessence, 2005.
13 Woda A, Pionchon P: A unified concept of idiopathic orofacial pain: clinical features. J Orofac Pain 1999;13:172–184.
14 Stohler CS: Muscle-related temporomandibular disorders. J Orofac Pain 1999;13:273–284.
15 Lavigne G, Woda A, Truelove E, Ship E, Dao T, Goulet J-P: Mechanisms associated with unusual orofacial pain. J Orofac Pain 2005;19:9–21.
16 Palla S: Anatomy and pathophysiology of the temporomandibular joint; in Klineberg I, Jagger R (eds): Occlusion and Clinical Practice. Edinburgh, Wright, 2004, pp 31–42.
17 Hylander WL: Functional anatomy and biomechanics of the masticatory apparatus; in Laskin DM, Greene CS, Hylander WL (eds): Temporomandibular Disorders – An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006, pp 3–34.
18 Asaki S, Sekikawa M, Kim YT: Sensory innervation of temporomandibular joint disk. J Orthop Surg 2006;14:3–8.
19 Sessle BJ: Sensory and motor neurophysiology of the TMJ; in Laskin DM, Greene CS, Hylander WL (eds): Temporomandibular Disorders – An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006, pp 69–88.

20 Haeuchi Y, Matsumoto K, Ichikawa H, Maeda S: Immunohistochemical demonstration of neuropeptides in the articular disk of the human temporomandibular joint. Cells Tissues Organs 1999;164:205–211.
21 Svensson P, Sessle BJ: Orofacial pain; in Miles T, Nauntofte B, Svensson P (eds): Clinical Oral Physiology. Copenhagen, Quintessence, 2004, pp 93–139.
22 Hugger A: Arthralgie der Kiefergelenke; in Hugger A, Göbel H, Schilgen M (eds): Gesichts- und Kopfschmerzen aus interdisziplinärer Sicht. Heidelberg, Springer, 2006, pp 77–90.
23 Lam DK, Sessle BJ, Cairns BE, Hu JW: Neural mechanisms of temporomandibular joint and masticatory muscle pain: a possible role for peripheral glutamate receptor mechanisms. Pain Res Manag 2005;10:145–152.
24 Martel-Pelletier J: Pathophysiology of osteoarthritis. Osteoarthritis Cartilage 2003;12(suppl A): S31–S33.
25 Baici A, Lang A, Zwicky R, Müntener K: Cathepsin B in osteoarthritis: uncontrolled proteolysis in the wrong place. Semin Arthritis Rheum 2005;34(suppl 2):24–28.
26 Suárez-Almazor ME, Osiri M, Emery P: Rheumatoid arthritis; in Tugwell P (ed): Evidence-Based Rheumatology. London, BMJ Books, 2004, pp 243–294.
27 van den Berg WB, van der Kraan PM, van Beuningen HM: Synovial mediators of cartilage damage and repair in osteoarthritis; in Brandt KD, Doherty M, Lohmander LS (eds): Osteoarthritis, ed 2. Oxford, Oxford University Press, 2003, pp 147–155.
28 Kopp S: Neuroendocrine, immune, and local responses related to temporomandibular disorders. J Orofac Pain 2001;15:9–28.
29 Kacena MA, Merrel GA, Konda SR, Wilson KM, Xi Y, Horowitz MC: Inflammation and bony changes at the temporomandibular joint. Cells Tissues Organs 2001;169:257–264.
30 Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT: Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). J Dent Res 2002;81:284–288.
31 Kamisaka M, Yatani H, Kuboki T, Matsuka Y, Minakuchi H: Four-year longitudinal course of TMD symptoms in an adult population and the estimation of risk factors in relation to symptoms. J Orofac Pain 2000;14:224–232.
32 de Leeuw R: Psychosocial Aspects and Symptom Characteristics of Craniomandibular Dysfunction; thesis, Utrecht University, 1993.
33 Lindroth JE, Schmidt JE, Carlson CR: A comparison between masticatory muscle pain patients and intracapsular pain patients on behavioral and psychosocial domains. J Orofac Pain 2002;16: 277–283.
34 Milam SB: Pathogenesis of degenerative temporomandibular joint arthritides. Odontology 2005;93: 7–15.
35 Milam SB: TMJ osteoarthritis; in Laskin DM, Greene CS, Hylander WL (eds): Temporomandibular Disorders – An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006, pp 105–123.
36 Brooks D, Wilson L, Kelsey C: Accuracy and reliability of 'specialized' physical therapists in auscultating tape-recorded lung sounds. Physiotherapy 1993;45:21–24.
37 Koran LM: The reliability of clinical methods, data and judgements. N Engl J Med 1975;293: 642–646.
38 Haas M: Interexaminer reliability for multiple diagnostic test regimens. J Manip Physiol Ther 1991;14:95–103.
39 Haas M: Statistical methodology for reliability studies. J Manip Physiol Ther 1991;14:119–132.
40 Steenks MH, de Wijer A, Bosman F: Orthopaedic diagnostic tests for temporomandibular and cervical spine disorders. J Back Musculoskelet Rehabil 1996;6:135–153.
41 Huddleston Slater J, Visscher C, Lobbezoo F, Naeije M: The intra-articular distance within the TMJ during free and loaded closing movements. J Dent Res 1999;78:1815–1820.
42 Lobbezoo-Scholte AM, Steenks MH, Faber JAJ, Bosman F: Diagnostic value of orthopaedic tests in patients with craniomandibular disorders. J Dent Res 1993;72:1443–1453.
43 Brooks SL: Imaging of the temporomandibular joint: a position paper of the American Academy of Oral and Maxillofacial Radiology. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:609–618.

44 Jaspers GWC, Stegenga B: Trigeminusneuralgie door een neurinoom van de nervus acusticus. De noodzaak van beeldvormend onderzoek. Ned Tijdschr Tandheelkd 2005;112:231–233.
45 Emschoff R, Brandlmaier I, Bertram S, Rudisch A: Magnetic resonance imaging of osteoarthrosis and effusion in patients with unilateral temporomandibular joint pain. Int J Oral Maxillofac Surg 2002;31:598–602.
46 Whitney CW, Von Korff M: Regression to the mean in treated versus untreated chronic pain. Pain 1992;50:281–285.
47 Kropmans TJB: Clinical Decision Making in Temporomandibular Joint Treatment Planning and Evaluation; thesis, Groningen University, 2001.
48 Fricton JR, Kroening RJ, Hathaway KM (eds): TMJ and Craniofacial Pain: Diagnosis and Management. St. Louis, Ishiyaku Euro-America, 1988.
49 Fricton JR, Olsen T: Predictors of outcome for treatment of temporomandibular disorders. J Orofac Pain 1996;10:54–65.
50 De Leeuw JRJ, Ros WJG, Steenks MH, Scholte AM, Bosman F, Winnubst JAW: Multidimensional evaluation of craniomandibular dysfunction. II. Pain assessment. J Oral Rehabil 1994;21: 515–532.
51 De Leeuw JRJ, Steenks MH, Ros WJG, Scholte AM, Bosman F, Winnubst JAW: Treatment outcome assessment in patients with craniomandibular dysfunction. J Oral Rehabil 1994;21: 655–666.
52 De Leeuw JRJ, Ros WJG, Steenks MH, Scholte AM, Bosman F, Winnubst JAM: Craniomandibular dysfunction: patient characteristics related to treatment outcome. J Oral Rehabil 1994;21: 667–678.
53 Leeuw R, Boering G, Stegenga B, de Bont GM: Symptoms of temporomandibular joint osteoarthrosis and internal derangement 30 years after non-surgical treatment. Cranio 1995;3: 81–88.
54 Forssell H, Kalso E: Application of principles of evidence-based medicine to occlusal treatments for temporomandibular disorders: are there lessons to be learned? J Orofac Pain 2004;18:9–22.
55 Forssell H, Kalso E, Koskela P, Vehmanen R, Puukka P, Alanen P: Occlusal treatments in temporomandibular disorders: a qualitative systematic review of randomized controlled trials. Pain 1999;83:549–560.
56 Clark GT: Application of principles of evidence-based medicine to occlusal treatments for temporomandibular disorders: are there lessons to be learned? Critical commentaries. J Orofac Pain 2004;18:23–24.
57 Klineberg I: Application of principles of evidence-based medicine to occlusal treatments for temporomandibular disorders: are there lessons to be learned? Critical commentaries. J Orofac Pain 2004;18:24–27.
58 Nilner M: Application of principles of evidence-based medicine to occlusal treatments for temporomandibular disorders: are there lessons to be learned? Critical commentaries. J Orofac Pain 2004;18:27–30.
59 Al-Ani MZ, Davies SJ, Gray RJM, Sloan P, Glenny AM: Stabilization splint therapy for temporomandibular pain dysfunction syndrome. Cochrane Database Syst Rev 2004;1:CD002778.
60 Türp JC, Komine F, Hugger A: Efficacy of stabilization splints for the management of patients with masticatory muscle pain: a qualitative systematic review. Clin Oral Invest 2004;8:179–195.
61 Dahlström L, Carlsson GE, Carsson SG: Comparison of effects of electromyographic biofeedback and occlusal splint therapy on mandibular dysfunction. Scand J Dent Res 1982;90:151–156.
62 Lundh H, Westesson P-L, Kopp S, Tillström B: Anterior repositioning splint in the treatment of temporomandibular joints with reciprocal clicking: comparison with a flat occlusal splint and untreated control group. Oral Surg Oral Med Oral Pathol 1985;60:131–136.
63 Lundh H, Westesson P-L, Jisander S, Eriksson L: Disk-repositioning onlays in the treatment of temporomandibular joint disk displacement: comparison with a flat occlusal splint and with no treatment. Oral Surg Oral Med Oral Pathol 1988;66:155–162.
64 List T, Helkimo M, Andersson S, Carlsson GE: Acupuncture and occlusal splint therapy in the treatment of craniomandibular disorders. Part I. A comparative study. Swed Dent J 1992;16:125–141.
65 List T, Helkimo M: Acupuncture and occlusal splint therapy in the treatment of craniomandibular disorders. II. A 1-year follow-up study. Acta Odont Scand 1992;50:375–385.

66 Lundh H, Westesson P-L, Eriksson L, Brooks SL: Temporomandibular joint disk displacement without reduction. Treatment with flat occlusal splint versus no treatment. Oral Surg Oral Med Oral Pathol 1992;73:655–658.
67 Linde C, Isacsson G, Jonsson BG: Outcome of 6-week treatment with transcutaneous electric nerve stimulation compared with splint on symptomatic temporomandibular joint disk displacement without reduction. Acta Odontol Scand 1995;53:92–98.
68 Ekberg EC, Vallon D, Nilner M: Occlusal appliance therapy in patients with temporomandibular disorders. A double-blind controlled study in a short-term perspective. Acta Odont Scand 1998;56: 122–128.
69 Werndahl L, Seeman L, Carlsson GE: Bettslipning – rörelsebehandling. En jämförande studie av två behandlingsmethoder för patienter med käkledsbesvär. Tandläkartidningen 1971;3: 560–565.
70 Wenneberg B, Nystrom T, Carlsson GE: Occlusal equilibration and other stomatognathic treatment in patients with mandibular dysfunction and headache. J Prosthet Dent 1988;59:478–483.
71 Vallon D, Ekberg EC, Nilner M, Kopp S: Short-term effect of occlusal adjustment on craniomandibular disorders including headaches. Acta Odont Scand 1991;49:89–96.
72 Vallon D, Ekberg EC, Nilner M, Kopp S: Occlusal adjustment in patients with craniomandibular disorders including headaches. A 3- and 6-months follow-up. Acta Odont Scand 1995;53:55–59.
73 Tsolka P, Morris RW, Preiskel HW: Occlusal adjustment therapy for craniomandibular disorders: a clinical assessment by a double-blind method. J Prosthet Dent 1992;68:957–964.
74 Antczak AA, Tang J, Chalmers TC: Quality assessment of randomised control trials in dental research. I. Methods. J Periodont Res 1986;21:305–314.
75 Van der Glas HW, Buchner R, van Grootel RJ: Vergelijking tussen behandelingsvormen bij myogene temporomandibulaire dysfunctie. Ned Tijdschr Tandheelkd 2000;107:505–512.
76 Michelotti A, Steenks MH, Farella M, Parisini F, Cimino R, Martina R: The extravalue of home physical therapy regime versus patient education only for the treatment of myofascial pain of the jaw muscles: a randomized clinical trial. J Orofac Pain 2004;18:114–125.
77 Koh H, Robinson PG: Occlusal adjustment for treating and preventing temporomandibular joint disorders. Cochrane Database Syst Rev 2003;1:CD003812.
78 Ekberg EC, Kopp S, Åkerman S: Diclofenac sodium as an alternative treatment of temporomandibular joint pain. Acta Odontol Scand 1996;54:154–159.
79 Minakuchi H, Kuboki T, Matsuka Y, Maekawa K, Yatani H, Yamashita A: Randomized controlled evaluation of non-surgical treatments for temporomandibular joint anterior disk displacement without reduction. J Dent Res 2001;80:924–928.
80 Yuasa H, Kurita K: Treatment Group on Temporomandibular Disorders: Randomized clinical trial of primary treatment for temporomandibular disk displacement without reduction and without osseous changes: a combination of NSAIDs and mouthopening exercise versus no treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:671–675.
81 Feine J, Lund JP: An assessment of the efficacy of physical therapy and physical modalities for the control of chronic musculoskeletal pain. Pain 1997;71:5–23.
82 McNeely ML, Olivo SA, Magee DJ: A systematic review of the effectiveness of physical therapy interventions for temporomandibular disorders. Phys Ther 2006;86:710–725.
83 Medlicott MS, Harris SR: A systematic review of the effectiveness of exercise, manual therapy, electrotherapy, relaxation training, and biofeedback in the management of temporomandibular disorder. Phys Ther 2006;86:955–973.
84 Declarations of principle and position statements. World Confederation for Physical Therapy (WCPT), London, 1995.
85 International Classification of Functioning, Disability, and Health (ICF): ICF full version. Geneva, World Health Organization, 2001.
86 Steiner WA, Ryser L, Huber E, Uebelhart D, Aeschlimann A, Stucki G: Use of the ICF model as a clinical problem-solving tool in physical therapy and rehabilitation medicine. Phys Ther 2002;82: 1098–1107.
87 Steenks MH, de Wijer A: Einige Fallstudien zur therapeutischen Mehrfachstrategie; in Steenks MH, de Wijer A (eds): Kiefergelenksfehlfunktionen aus physiotherapeutischer und zahnmedizinischer Sicht: Diagnose und Therapie. Berlin, Quintessenz, 1991, pp 193–262.

88 Michelotti A, de Wijer A, Steenks MH, Farella M: Home exercise regimes for the management of non-specific temporomandibular disorders. J Oral Rehabil 2005;32:779–785.
89 Carmeli E, Sheklow SL, Bloomenfield I: Comparative study of repositioning splint therapy and passive manual range of motion techniques for anterior displaced temporomandibular discs with unstable excursive reduction. Physiotherapy 2001;87:26–36.
90 Yoda T, Sakamoto I, Imai H, Honma Y, Shinjo Y, Takano A, Tsukahara H, Morita S, Miyamura J, Yoda Y, Sasaki Y, Tomizuka K, Takato T: A randomized controlled trial of therapeutic exercise for clicking due to disk anterior displacement with reduction in the temporomandibular joint. Cranio 2003;21:10–15.
91 Minagi S, Nozaki S, Sato T, Tsuru H: A manipulation technique for treatment of anterior disk displacement without reduction. J Prosthet Dent 1991;65:686–691.
92 Moore CD, McQuay HJ, Fairman F, Tramèr M, Leijon G: Transcutaneous electrical nerve stimulation (TENS) for chronic pain. Cochrane Database Syst Rev 2000;4:CD003222. DOI: 10.1002/14651858.CD003222.
93 Brosseau L, Robinson V, de Bie R, Gam A, Harman K, Morin M, Shea B, Tugwell P: Low level laser therapy (classes I, II and III) for treating osteoarthritis. Cochrane Database Syst Rev 2005;4:CD002049.
94 Kulekcioglu S, Sivirioglu K, Ozcan O, Parlak M: Effectiveness of low-level laser therapy in temporomandibular disorder. Scand J Rheumatol 2003;32:114–118.
95 Bjordal JM, Couppé C, Chow R, Tunér J, Ljunggren EA: A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. Aust J Physiother 2003;49:107–116.
96 Jadad AR, Moore RA, Carroll D, et al: Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.

Michel H. Steenks, DDS, PhD
University Hospital Utrecht, Division Surgical Sciences
Department of Oral-Maxillofacial Surgery, Prosthodontics and Special Dental Care
Clinic for Temporomandibular Disorders and Orofacial Pain
PO Box 85060, NL–3508 AB Utrecht (The Netherlands)
Tel. +31 30 253 3534, Fax +31 30 253 5537, E-Mail M.H.Steenks@umcutrecht.nl

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 153–164

Neuralgic and Idiopathic Facial Pain

Pathophysiology and Management

Claudia Sommer

Neurologische Klinik der Universität Würzburg, Würzburg, Germany

Abstract

In patients with facial pain, making the correct diagnosis is essential to avoid erroneous diagnostic and therapeutic measures. Most importantly, primary facial pain syndromes and symptomatic facial pain due to an underlying disease have to be distinguished. *Trigeminal neuralgia* is easily recognized by the typical history and pain character reported by the patient. The treatment of first choice is carbamazepine. When pharmacological treatment fails, surgical options are available. Other cranial neuralgias are rare; they are recognized by the respective location and radiation of the pain. *Idiopathic persistent facial pain* should only be diagnosed after thorough exclusion of all known primary and symptomatic facial pain syndromes. Management is difficult and consists of tricyclic antidepressants, behavioral therapy and of avoiding iatrogenic damage.

Whereas some of the neuralgic forms of orofacial pain can be very well defined, the term 'idiopathic' already indicates that facial pain in some patients is difficult to understand and to classify. However, most of these entities are clinically well defined and can be diagnosed after a careful patient history. The correct diagnosis is important, since some of the neuralgic or neuropathic facial pain syndromes respond to very specific treatment modalities only. If patients are undiagnosed, this may entail an odyssey from one physician to the next lasting for years.

Facial Neuralgias

There is no good definition of neuralgia. The International Association for the Study of Pain defines it as pain in the territory of one nerve. More comprehensive definitions include the paroxysmal character and a high intensity of

Table 1. International Headache Society diagnostic criteria of trigeminal neuralgia [1]

- Paroxysmal attacks of pain lasting from a fraction of a second to 2 min, affecting one or more divisions of the trigeminal nerve and
- Pain has at least one of the following characteristics:
  (1) intense, sharp, superficial or stabbing
  (2) precipitated from trigger areas or by trigger factors
- Attacks are stereotyped in the individual patient
- There is no clinically evident neurological deficit
- The pain cannot be attributed to another disorder

pain. Traditionally, the pain is thought to be independent of a structural lesion, although improved diagnostic methods are increasingly revealing pathological findings at the nerves in question. Theoretically, each cranial nerve carrying sensory fibers may be prone to cause neuralgia. Most often, trigeminal neuralgias occur, followed by occipital and glossopharyngeal neuralgias and neuralgias of the intermediate nerve and of the superior laryngeal nerve. Furthermore, there are many cases of postherpetic neuralgia in the trigeminal area.

Trigeminal Neuralgia

Clinical Features

Trigeminal neuralgia is characterized by brief attacks of unilateral pain in the territory of one or more branches of the trigeminal nerve; see table 1 for a definition. In the beginning, there may be periods of spontaneous remission lasting for weeks to months [2]. The pain attacks are characterized as lancinating, stabbing or electric-shock-like, they can occur spontaneously or may be triggered by trivial stimuli, such as touching the skin, chewing, talking, brushing the teeth or shaving. Most frequently, the second or third branch of the trigeminal nerve is affected. The attacks often occur in clusters, which makes some patients report them as lasting for much longer than seconds. Out of fear of new attacks, elderly patients may avoid fluid and food intake and may present in the clinic in a dehydrated, often confused state. Some patients become suicidal.

Trigeminal neuralgia has an overall prevalence of 1:30,000 and occurs mostly in elderly patients, more often in women than in men. Younger patients with trigeminal neuralgia may have an underlying disease, such as multiple sclerosis, where trigeminal neuralgia occurs in 1–5%. Other symptomatic causes include tumors of the cerebellar pontine angle, aneurysms or ischemic

brain infarcts [3]. In these conditions, there are often continuous pain and sensory deficits in addition to the neuralgic pain.

The diagnosis is mainly based on a detailed history and the patient's description of the pain. Patients will localize the pain into the territory of one of the branches of the trigeminal nerve. Pain attacks typically last for seconds, and the patients are pain free between attacks. Touching the skin can trigger attacks. The neurological examination should not reveal abnormalities in the trigeminal innervation. If sensory deficits are present, a trigeminal neuropathy ('symptomatic trigeminal neuralgia'), i.e. overt damage of the nerve, has to be suspected and further diagnostic tests should be performed. This is also necessary if the pain is persistent between attacks, if there are bilateral symptoms or if the patient is not elderly. A cranial MRI scan should be performed to exclude a tumor, an aneurysm, a cerebral infarct or an inflammatory demyelinating lesion, such as in multiple sclerosis. The MRI scan can also show the neurovascular contact, which is often present in typical trigeminal neuralgia. A sensitivity of 100% can be reached using special MRI techniques [4, 5]. Specificity is lower, since about 8% of asymptomatic controls also have the finding of vascular contacts so that this finding is only relevant in the presence of clinical symptoms. Neurophysiological tests, e.g. the blink reflex, the masseter reflex and evoked potentials of the trigeminal nerve, may also substantiate a lesion of the trigeminal nerve. If in addition multiple sclerosis is suspected, an investigation of the cerebrospinal fluid and further neurophysiological tests are needed.

Pathophysiology

The pain attacks are the consequence of dysfunction of the trigeminal nerve or its central connections. The typical trigeminal neuralgia of the elderly is caused by demyelination of the trigeminal root at its entrance into the pons [6]. In this region, CNS tissue extends along the nerve root for a few millimeters so that the pathology takes place in CNS tissue [3]. CNS myelin, produced by astrocytes, is more vulnerable to compression than peripheral nerve myelin. The most frequently found cause of demyelination is compression by an arteriosclerotic and elongated artery, mostly the superior cerebellar artery. This leads to direct membrane-to-membrane contact of axons, to spontaneous activity and sensitization to pressure by the overlying artery. Ephaptic impulse propagation between fibers mediating tactile impulses and nociceptors has been proposed, possibly explaining the triggering of pain. When the compression is stopped operatively, pain mostly ceases immediately. This is explained by reduction of ectopic impulse generation [3]. The progressive demyelination may also lead to axonal damage so that in the long run trigeminal neuralgia can induce spontaneous continuous pain. At this stage, the success of neurovascular decompression is reduced [7].

Treatment

The attacks in trigeminal neuralgia are too short to be treated by acute medication. Medical treatment is thus aimed at reducing the number of attacks. Drugs acting at voltage-gated sodium channels seem to be most efficient. Carbamazepine is still regarded the drug of first choice. It is the only drug that has been tested in several placebo-controlled randomized controlled trials. Dosage and alternative drugs are given in table 2. The initial response rate to carbamazepine is almost 90%. However, a dose increase is necessary in the course of the disease in some patients, and side effects may preclude reaching an efficient dose. If a rapid onset of action is needed, phenytoin can be given intravenously (off-label use) at 250 mg b.i.d. after exclusion of conduction blocks by electrocardiography. Newer drugs regarded as second-line treatment are lamotrigine, which has been used as an add-on medication in one small trial, and gabapentin, which has been efficient in open label trials. There are case reports on success with valproic acid, oxcarbazepine and topiramate, but no data from randomized controlled trials are available yet. Misoprostol was useful in a small case series of patients with multiple sclerosis.

Interventional Treatment

If medical treatment is not sufficient or not tolerable, interventional treatment is indicated. The principal methods are microvascular decompression in the cerebellopontine angle, percutaneous procedures at the ganglion gasseri and radiosurgical treatment.

Following the hypothesis of neurovascular compression, the operation named after Peter Jannetta [8] is regarded to address the underlying cause of trigeminal neuralgia. Patients with good general health who can receive general anesthesia are eligible. The trigeminal root is decompressed via a retrosigmoidal approach through the occipital fossa, the trigeminal root is prepared, and, if a compressing artery can be identified, it is separated from the nerve. Short- and long-term success is good, with acute improvement in 87–98% of patients and long-term results with 60% success rates at 8 years. The rate of complications is 1–2%, with rare serious complications [9].

Older patients in poor general health can be treated with selective percutaneous high-frequency thermolesion of the ganglion gasseri [10]. Under radiographic control, a needle is introduced into the foramen ovale. Radiofrequency stimulation is used to selectively destroy the nociceptive trigeminal fibers. This method can also be helpful in patients with multiple sclerosis [11]. Numbness and dysesthesias may occur as side effects, and more rarely keratitis, anesthesia dolorosa and dysfunction of masticatory muscles. The relapse rate is 20% in 10 years, but the procedure can be repeated. Stereotactic radiosurgery has an

Table 2. Medical treatment of trigeminal neuralgia

Generic drug name	Dose	Efficacy	Evidence	Side effects
CBZ	600–1,200 (–1,600) mg start slowly, give 2 doses of a retarded preparation	Initial success rate up to 90%	I	Sedation, ataxia, nausea, cognitive disturbances in the elderly, allergies, hyponatremia, arrhythmias, neutropenia
Oxcarbazepine	900–1,800 mg	Probably like CBZ	II	Fewer than CBZ
Baclofen	15–80 mg, start slowly	Weaker than CBZ	II	Sedation, nausea, muscle weakness
Lamotrigine	400 mg, start slowly	Only tested in combination with CBZ or phenytoin	II	Allergies, sedation, nausea, dizziness
Gabapentin	900–2,400 mg	Open trials	II	Sedation, dizziness, edema
Misoprostol	200–400 mg	Open trial	III	Abdominal pain, nausea
Phenytoin	300 mg single evening dose (intravenous 2 × 250/day)	Rapid onset of action when given intravenously	IV	Sedation, ataxia, nausea, dysarthria, chorea, gingival hypertrophy, hirsutism, vitamin D deficiency
Valproic acid	600–1,200 mg	Open trial	IV	Nausea, vomiting, weight gain, tremor, confusion

CBZ = Carbamazepine. Evidence = Classes of evidence; class I = several adequately powered prospective, randomized, controlled clinical trials with masked outcome assessment in a representative population; class II = one adequately powered prospective, randomized, controlled clinical trial or a prospective matched-group cohort study in a representative population with masked outcome assessment; class III = all other controlled trials in a representative population, where outcome assessment is independent of patient treatment; class IV = evidence from uncontrolled studies, case series, case reports or expert opinion.

initial success rate of 86% and one of 75% at 33 months [12]. Complications occur in 10% of cases.

Glossopharyngeal Neuralgia

Pain is unilateral in the base of the tongue, the tonsillar fossa, the pharynx or between the mandible and the ear. Talking, swallowing, chewing, coughing

and yawning are typical triggers. Pain on touching the tonsils is regarded as being pathognomonic but is not always present. Rushton et al. [13] described 217 patients, which they had seen between 1922 and 1977, with many spontaneous remissions. Syncopes may occur, which are thought to be caused by pathological discharges in the motor vagus nucleus or of sensory fibers in the carotid sinus [14]. Treatment is similar to that of trigeminal neuralgia, including neurovascular decompression [15]. Since glossopharyngeal neuralgia often occurs as a symptom of an underlying disease, imaging and endoscopy have to be used to exclude tumors or other lesions in the area.

Other Cranial Neuralgias

Neuralgia of the intermediate nerve is a rare neuralgia where the pain is localized deep in the ear. The trigger is the posterior wall of the auditory canal. Treatment is similar to that of trigeminal neuralgia. It has been questioned whether the intermediate nerve is really the source of the pain.

Neuralgia of the superior laryngeal nerve is also rare. The pain is localized in the lateral neck. Triggers are swallowing, loud speaking or turning of the head [16]. There are symptomatic forms with diseases of the larynx. Carbamazepine may be helpful. In refractory cases, the transection of the internal branch of the nerve has been used [14].

Occipital neuralgia occurs in the territory of the major or minor occipital nerve. Symptomatic forms are frequently encountered; hence, a thorough local examination is necessary. Blockade of the nerve with a local anesthetic can be useful [17].

Postherpetic neuralgia may occur in branches of the trigeminal nerve, most often in the ophthalmic branch. The diagnosis is clear if a history of a typical varicella-zoster rash is given. Therapy follows the general guidelines for treatment of neuropathic pain [18].

Short-Lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing

This disorder belongs to the trigeminal autonomic headaches and is listed here because it may be confounded with trigeminal neuralgia. Patients with SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) complain of short-lasting pain attacks (seconds to minutes) localized in the orbita or the supraorbital or temporal regions. The pain is stabbing or pulsating. The number of attacks per day ranges from a few

Table 3. International Headache Society diagnostic criteria of persistent idiopathic facial pain [1]

- Pain in the face, present daily and persisting for all or most of the day
- Pain is confined at the onset to a limited area on one side of the face, is deep and can be poorly localized
- Pain is not associated with sensory loss or other physical signs
- Investigations including X-ray of the face and jaws do not demonstrate any relevant abnormality

to several hundred. Accompanying symptoms are ipsilateral conjunctival injection, tearing, nasal congestion, rhinorrhea or eyelid edema. A few patients have been described in whom there is an overlap between SUNCT and trigeminal neuralgia. In these cases, the exact diagnosis is difficult. The distinction is important, because SUNCT most often does not respond to carbamazepine. Some patients respond to lamotrigine [19, 20]. Associated lesions generating a symptomatic SUNCT syndrome may be arterovenous malformations in the posterior fossa, brainstem ischemic lesions or congenital bone malformations in the posterior skull [21].

Persistent Idiopathic Facial Pain

Clinical Features

Persistent idiopathic facial pain (formerly: atypical facial pain) is defined as continuous facial pain that does not have the characteristics of any of the cranial neuralgias and is not attributed to another disorder. The pain is mostly unilateral and is described as dull, sore or burning. There should be no abnormal physical findings on examination, i.e. no sensory loss in the affected region. It is mandatory that causes for symptomatic facial pain are excluded, including by X-ray of the face and jaws. Pain may be initiated by surgery or injury to the face, teeth or gums, but persists without any demonstrable local cause. A pathological local finding excludes the diagnosis; see table 3 for definition.

The prevalence of persistent idiopathic facial pain is unknown. It is assumed that 60–70% of the patients are middle-aged women [22]. In specialized pain centers, patients with persistent idiopathic facial pain are seen slightly more frequently than patients with trigeminal neuralgia. Most patients are primarily treated by a dentist or orthodontist. The patients describe continuous pain, which may vary in intensity but usually does not present in attacks. The pain is mostly unilateral but may change sides. It is not confined to the territory

of a trigeminal branch. Pain is most often localized to the upper jaw and may spread to the region of the eye, nose, cheek, temple and lower jaw. Sometimes, the pain is localized in one tooth and will then be classified as atypical odontalgia. While the pain is present all day long, it is usually absent at night and sleep is not disturbed. The pain is described as dull, boring and sore. Sometimes, affective descriptors such as 'unbearable' and 'agonizing' are used [23], although pain intensity is rated as intermediate. There are no attacks of shooting pain like in the neuralgias and no trigger zones. Sometimes patients do report attack-like increases in pain, which does not exclude the diagnosis [24]. There may be dysesthesias, paresthesias and a subjective feeling of numbness, but no objective sensory deficits or other local pathological signs. Some patients perceive a subjective swelling of part of the face, which is usually not visible to the examiner.

In many cases, there is a history of facial trauma or of surgery in the jaws, nose or nasal sinuses. If pain was present before surgery, it may be increased afterwards [25, 26]. Unfortunately, there are no epidemiological data on the incidence of persistent pain after facial surgery. Some of the patients have pain in additional locations, such as chronic back or neck pain, myofascial pain, migraine, irritable bowel syndrome or dysmenorrhea [27]. Therefore, it is necessary to ask for additional sites of pain when taking the history. A whole-body pain drawing is useful to discover widespread pain or other painful comorbidities [28].

The prevalence of psychiatric disorders is increased in patients with persistent idiopathic facial pain. One study found 16% affective disorders, 15% somatoform disorders, psychosis in 6% and related disorders in 16% [29]. Since similar figures have been reported in other chronic pain syndromes, a causal relationship cannot necessarily be assumed.

Pathophysiology

The pathogenesis of persistent idiopathic facial pain is unclear. Most likely, persistent idiopathic facial pain is a syndrome comprising several different etiologies. For a long time, a psychogenic origin was assumed [22]. The depletion of central serotonin and opioid deposits has been implied and the pathophysiology has been paralleled to that of depression [30]. However, tricyclic antidepressants are only efficient in some of the patients. Multiple operations may lead to injury of terminal nerve fibers so that some authors regard persistent idiopathic facial pain as a variety of phantom pain. However, signs of structural damage to the trigeminal nerve preclude the diagnosis, and a trigeminal neuropathy should be diagnosed instead.

Neurophysiological techniques, including the blink reflex and the masseter reflex, may further help to distinguish patients with trigeminal neuropathy

(i.e. damage of the trigeminal nerve) from those with a hyperreactive trigeminal nerve and those with normal findings [31]. In a positron emission tomography study including 6 patients with persistent idiopathic facial pain, the patients had higher blood flow in the anterior cingulum and lower blood flow in the prefrontal cortex compared to controls, when heat stimuli were applied to the dorsum of the hand. This pattern of activation was interpreted as 'hyperemotional' reaction to sensory information and as a hint to deficits in the inhibitory system [32]. In a further positron emission tomography study with 7 patients, an increased D_2 receptor density in the left putamen was found [33]. The relevance of this finding will have to be confirmed in larger cohorts.

Diagnosis

The diagnosis depends on the patient history and normal findings on examination. When taking the history, the course and duration of the disease, character and frequency of pain, past and present attempts at treatment as well as previous surgery and its outcome should be asked for. The McGill Pain Questionnaire may be of additional help to distinguish between different types of facial pain [23, 34]. It is important to recognize affective descriptions that may point to a psychiatric comorbidity. A pain drawing is useful to recognize further manifestations of pain and a possible generalized pain syndrome.

Neurophysiological recordings of the blink and masseter reflexes may recognize a trigeminal lesion [31]. Further apparative investigations may be needed to exclude causes of symptomatic facial pain.

Management

In symptomatic forms of facial pain, the underlying cause should be treated, if possible. The most important point in idiopathic facial pain is not to induce further damage. Patients should be informed about the chronic, albeit benign nature of the disorder. Surgical and dental procedures should be avoided, even if patients ask for them, unless there is an organic indication for such an operation. Pharmacological treatment should be tried, but is empirical due to the paucity of randomized controlled trials. Drugs that had a moderate effect in trials are the antidepressants phenelzine and dothiepine, which are not widely available. According to clinical experience, tricyclic antidepressants have the best success rate. Therapy is initiated with low nighttime doses and is later switched to a retarded formulation. Anticonvulsants like carbamazepine, oxcarbazepine and gabapentin have been tried, sometimes in combination with an antidepressant (table 4).

It is important to reduce the medication after an adequate trial (2 months in adequate doses) if it is not successful. Local application of capsaicin cream can

Table 4. Treatment of persistent idiopathic facial pain

Drug/treatment	Dose
Amitriptyline (slow release)	10–100 mg/day, give largest dose at night time
Clomipramine	25–150 mg/day
Doxepine	10–100 mg/day, give largest dose at nighttime
Gabapentin	1,200–2,400 mg/day in 3 doses
Carbamazepine (slow release)	400–1,200 mg/day in 2 doses
Oxcarbazepine	600–1,800 mg/day in 2 doses
Transcutaneous electrical stimulation	
Behavioral therapy	

No class I–II evidence was found for any of these treatments.

be tried; there are, however, only open trials [35]. Transcutaneous electrical stimulation gave some improvement in an open study [36]. Behavioral therapy is recommended to reduce fear, to help patients obtain a more realistic self-judgment and to better cope with pain.

References

1 Headache Classification Committee of the International Headache Society: The International Classification of Headache Disorders, ed 2. Cephalalgia 2004;24(suppl 1):1–160.
2 Nurmikko TJ, Jensen TS: Trigeminal neuralgia and other facial neuralgias; in Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA (eds): The Headaches. Philadelphia, Lippincott Williams & Wilkins, 2006, pp 1053–1062.
3 Love S, Coakham HB: Trigeminal neuralgia: pathology and pathogenesis. Brain 2001;124: 2347–2360.
4 Meaney JF, Eldridge PR, Dunn LT, Nixon TE, Whitehouse GH, Miles JB: Demonstration of neurovascular compression in trigeminal neuralgia with magnetic resonance imaging: comparison with surgical findings in 52 consecutive operative cases. J Neurosurg 1995;83:799–805.
5 Patel NK, Aquilina K, Clarke Y, Renowden SA, Coakham HB: How accurate is magnetic resonance angiography in predicting neurovascular compression in patients with trigeminal neuralgia? A prospective, single-blinded comparative study. Br J Neurosurg 2003;17:60–64.
6 Devor M, Govrin-Lippmann R, Rappaport ZHN: Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. J Neurosurg 2002;96:532–543.
7 Tyler-Kabara EC, Kassam AB, Horowitz MH, Urgo L, Hadjipanayis C, Levy EI, Chang YFN: Predictors of outcome in surgically managed patients with typical and atypical trigeminal neuralgia: comparison of results following microvascular decompression. J Neurosurg 2002;96: 527–531.
8 Jannetta PJ: Outcome after microvascular decompression for typical trigeminal neuralgia, hemifacial spasm, tinnitus, disabling positional vertigo, and glossopharyngeal neuralgia. Clin Neurosurg 1997;44:331–383.

9 Nurmikko TJ, Eldridge PR: Trigeminal neuralgia – Pathophysiology, diagnosis and current treatment. Br J Anaesth 2001;87:117–132.
10 Sweet WH, Wepsic JG: Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1. Trigeminal neuralgia. J Neurosurg 1974;40:143–156.
11 Berk C, Constantoyannis C, Honey CR: The treatment of trigeminal neuralgia in patients with multiple sclerosis using percutaneous radiofrequency rhizotomy. Can J Neurol Sci 2003;30:220–223.
12 Kondziolka D, Lunsford LD, Flickinger JC: Stereotactic radiosurgery for the treatment of trigeminal neuralgia. Clin J Pain 2002;18:42–47.
13 Rushton JG, Stevens JC, Miller RH: Glossopharyngeal (vagoglossopharyngeal) neuralgia: a study of 217 cases. Arch Neurol 1981;38:201–205.
14 Schmidt D, Malin J-P: Erkrankungen der Hirnnerven. Stuttgart, Thieme, 1995.
15 Patel A, Kassam A, Horowitz M, Chang YF: Microvascular decompression in the management of glossopharyngeal neuralgia: analysis of 217 cases. Neurosurgery 2002;50:705–710, discussion 710–711.
16 Bruyn GW: Superior laryngeal neuralgia. Cephalalgia 1983;3:235–240.
17 Kapoor V, Rothfus WE, Grahovac SZ, Amin Kassam SZ, Horowitz MB: Refractory occipital neuralgia: preoperative assessment with CT-guided nerve block prior to dorsal cervical rhizotomy. AJNR Am J Neuroradiol 2003;24:2105–2110.
18 Wallace MS: Diagnosis and treatment of neuropathic pain. Curr Opin Anaesthesiol 2005;18: 548–554.
19 D'Andrea G, Granella F, Ghiotto N, Nappi G: Lamotrigine in the treatment of SUNCT syndrome. Neurology 2001;57:1723–1725.
20 Gutiérrez-García JM: SUNCT syndrome responsive to lamotrigine. Headache 2002;42:823–825.
21 Trucco M, Mainardi F, Maggioni F, Badino R, Zanchin G: Chronic paroxysmal hemicrania, hemicrania continua and SUNCT syndrome in association with other pathologies: a review. Cephalalgia 2004;24:173–184.
22 Feinmann C, Harris M, Cawley R: Psychogenic facial pain: presentation and treatment. Br Med J (Clin Res Ed) 1984;288:436–438.
23 Melzack R, Terrence C, Fromm G, Amsel R: Trigeminal neuralgia and atypical facial pain: use of the McGill Pain Questionnaire for discrimination and diagnosis. Pain 1986;27:297–302.
24 Pfaffenrath V, Rath M, Keeser W, Pöllmann W: Atypischer Gesichtsschmerz – die Qualität der IHS-Kriterien und psychometrische Daten. Nervenarzt 1992;63:595–601.
25 Mock D, Frydman W, Gordon AS: Atypical facial pain: a retrospective study. Oral Surg Oral Med Oral Pathol 1985;59:472–474.
26 Jones NS, Cooney TR: Facial pain and sinonasal surgery. Rhinology 2003;41:193–200.
27 Feinmann C: Idiopathic orofacial pain: a multidisciplinary problem – The contribution of psychiatry and medicine to diagnosis and management; in Campbell JN (ed): Pain – An Updated Review. Seattle, IASP Press, 1996, pp 397–402.
28 Geis C, Feierabend S, Böhner W, Kares H, Schirmer P, Busche E, Schindler HJ, Siegert J, Hugger S, Türp JC, Hugger A, Sommer C: Vergleich von Akzeptanz und Informationsgehalt zweier Schemata zur Schmerzeinzeichnung bei Patienten mit orofazialen Schmerzen. Schmerz 2006;20:498–508.
29 Remick RA, Blasberg B: Psychiatric aspects of atypical facial pain. J Can Dent Assoc 1985;51: 913–916.
30 Lehmann HJ, Buchholz G: Atypische Gesichtsneuralgie oder depressiver Gesichtsschmerz? Fortschr Neurol Psychiatr 1986;54:154–157.
31 Jääskelainen SK, Forssell H, Tenovuo O: Electrophysiological testing of the trigeminofacial system: aid in the diagnosis of atypical facial pain. Pain 1999;80:191–200.
32 Derbyshire SW, Jones AK, Devani P, Friston KJ, Feinmann C, Harris M, Pearce S, Watson JD, Frackowiak RS: Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography. J Neurol Neurosurg Psychiatry 1994;57:1166–1172.
33 Hagelberg N, Forssell H, Aalto S, Rinne JO, Scheinin H, Taiminen T, Nagren K, Eskola O, Jaaskelainen SK: Altered dopamine D_2 receptor binding in atypical facial pain. Pain 2003;106:43–48.
34 Mongini F, Italiano M, Raviola F, Mossolov A: The McGill Pain Questionnaire in patients with TMJ pain and with facial pain as a somatoform disorder. Cranio 2000;18:249–256.

35 Vickers ER, Cousins MJ, Walker S, Chisholm K: Analysis of 50 patients with atypical odontalgia: a preliminary report on pharmacological procedures for diagnosis and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:24–32.
36 Eriksson MB, Sjölund BH, Sundbarg G: Pain relief from peripheral conditioning stimulation in patients with chronic facial pain. J Neurosurg 1984;61:149–155.

Prof. Dr. med. Claudia Sommer
Neurologische Klinik der Universität
Josef-Schneider-Strasse 11
DE–97080 Würzburg (Germany)
Tel. +49 931 201 23 763, Fax +49 931 201 23 697, E-Mail sommer@mail.uni-wuerzburg.de

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 165–186

Burning Mouth Syndrome

Pathophysiology and Management

Joanna Zakrzewska, Tara Renton

Institute of Dentistry, Barts and the London Queen Mary's School of Medicine and Dentistry, London, UK

Abstract

Burning mouth syndrome (BMS) is defined as intra-oral burning sensation for which no medical or dental causes can be found and in which the oral mucosa is of grossly normal appearance. It varies in prevalence from 0.7 to 15%, depending on the diagnostic criteria used, and it is found most commonly in female menopausal women. There is increasing evidence to show that BMS is primarily a neuropathic pain with secondary psychological features. Therefore, sensory testing may be crucial in the diagnostic process. Management remains difficult due to the lack of high-quality randomized controlled trials but should take a biopsychosocial approach. There is a regularly updated Cochrane systematic review on this topic. Topical therapies such as clonazepam may be beneficial. There is some evidence for the use of vitamins, such as α-lipoic acid, and antidepressants for longer-term use. Cognitive behaviour therapy may be beneficial. Essential for improved quality of life is reassurance that this is not a rare condition and does not lead to cancer. As this is a long-term condition, patients need to develop coping strategies.

Definition

The definition of burning mouth syndrome (BMS) has been controversial; 2 review articles in the 1990s suggested clearer criteria which would enable consistencies between studies to be achieved [1, 2]. There now appears to be more consistency, and the following definition seems to have become accepted: 'intra-oral burning sensation or other dysaesthesia for which no medical or dental causes can be found and in which the oral mucosa is of grossly normal appearance'. The word 'syndrome' is used because many patients will also have subjective dryness, paraesthesia and altered taste. The terminology, however,

remains varied and includes 'glossodynia', 'oral dysaesthesia', 'stomatodynia' and 'glossopyrosis'. The term 'burning mouth disorder' has also been proposed.

Epidemiology

The epidemiological data on BMS are generally poor due, in part, to a lack of strict adherence to diagnostic criteria. In a systematic review, Zakrzewska and Hamlyn [3] found that prevalence rates in general populations varied from 0.7 to 15%. The reason for the wide variation was due to the fact that most surveys carried out in the community relate to burning mouth as a symptom rather than the syndrome. In their survey in the Finnish community using a sample of 600 individuals, Tammiala-Salonen et al. [4] showed that if examination and investigations were included the prevalence changed from 15 to 1%. In specialized clinics, the prevalence tends to be high [5]. Most studies have shown that BMS affects predominantly females, with an increased prevalence with age and following menopause [3]. The natural history of BMS has not been clearly defined, and there are no reports of high-quality longitudinal cohort studies. Risk factors and high-risk patients have not been clearly identified although it would appear that postmenopausal women are at highest risk. The small study of Grushka et al. [6] suggested that at least partial spontaneous remission is seen in approximately half of these patients within 6–7 years. However, a recent study among 53 BMS patients attending a specialist centre in Italy showed only 3% of patients to have had a complete spontaneous remission within 5 years of the onset of BMS, while up to 30% had a moderate improvement; however, the study was using only pain relief as an outcome measure [7].

Aetiology and Pathophysiology

Bergdahl and Bergdahl [8] stated that the 'burning mouth syndrome (BMS) is a marker of illness and/or distress'. It is important to exclude secondary intra-oral burning sensation (secondary BMS) associated with systemic and local disorders [9]. In the absence of these disorders and the clinical features described below, a diagnosis of BMS may be made. The literature regarding BMS is replete with case series and poor-quality prospective studies that predominantly address the role of a plethora of variables in the aetiology of burning mouth. Many of the investigations have either no controls or they are poorly matched. A recent study has attempted to compare BMS with burning as a symptom, and many of the features discussed below have been evaluated. This has led to a debate about the aetiology of BMS.

Local Disorders

Disorders known to induce BMS-like symptoms include oral candidiasis, mucosal diseases such as lichen planus, galvanism, allergies, hyposalivation and xerostomia [10].

In some instances, candidal infections cause a burning sensation [11]. Although candidiasis can cause burning pain, its prevalence has not been found to be increased in patients with the disorder compared with control populations [12].

Mucosal diseases, including ulcerative or erosive lesions, periodontitis and geographic tongue, can cause discomfort of the mouth. A recent report attempted to quantify the appearance of changes in the fungiform papillae in relation to oral sensitivity and prevalence to atopy [13]. However, most studies have reported no significant changes in intra-oral soft- or hard-tissue mucosa [11, 14], which is now regarded as a key diagnostic criterion for BMS [9]. Similarly, atopy [13], chemical irritation and galvanic currents between dissimilar metals have not been found to be important causes of burning mouth [15].

Xerostomia has been suggested as an aetiological factor, in view of the higher incidence of this problem in patients with BMS [11, 14]. However, most salivary flow rate studies in affected patients have shown no decrease in unstimulated or stimulated salivary flow [16]. Some authors report increased salivary components, such as sodium, potassium, chlorine, calcium, amylase and IgA, in BMS patients when compared with controls [16]. These changes in salivary composition were associated with increased warm sensory thresholds. The cause of this is unknown, but the changes may result from altered sympathetic output related to stress, or from alterations in interactions between the cranial nerves serving taste and pain sensation [17].

Taste Function

Alterations in taste occur in as many as two thirds of patients and often include complaints of persistent tastes (bitter, metallic or both) or changes in the intensity of taste perception [18]. Al Quran et al. [19] report discomfort on application of capsaicin-containing Tabasco sauce; however, dysgeusic tastes accompanying oral burning are often reduced by stimulation with food [11]. Bartoshuk et al. [17] state that there is an increased prevalence of so-called supertasters (persons with enhanced abilities to detect taste) among patients with BMS. These supertasters may be more likely to be affected by BMS because of their higher density of taste buds, each of which is surrounded by a basket-like collection of nociceptive neurons of the trigeminal nerve [20]. It is further hypothesized [21, 22] that supertasters have a large number of fungiform papillae, which puts these individuals at greatest risk for developing BMS because of the increased innervation to the large number of papillae and the

potential for the greatest loss of inhibition if there is damage to this innervation. Taste sensation of the anterior two thirds of the tongue is supplied by the chorda tympani nerve, a branch of the facial nerve, while other modalities such as mechanical and thermal sensations are supplied by the lingual nerve, a branch of the mandibular division of the trigeminal nerve. It is possible that the chorda tympani and the lingual nerve exert mutual inhibitory homeostatic mechanisms and, in the case of an imbalance, BMS may occur [18, 22]. This model would also explain the lack of effect of hormone replacement therapy once neural symptoms are established.

General Factors

Systemic factors which may cause a burning sensation include: hormonal changes, haematinic deficiencies (vitamin B_{12}, folic acid or iron), diabetes mellitus, drugs (topical or systemic side-effects), auto-immune diseases and psychological disorders [11, 12, 14, 23].

With a reported incidence of over 50%, *psychogenic factors* have been consistently implicated in the aetiology of BMS [21, 24, 25]. BMS is stated to be 'conceptualized as a psychogenic physical continuum' [26, 27]. Several psychometric tools (Hospital Anxiety Depression Score, Personality Traits) have been used to identify anxiety, depression, personality and beliefs in BMS sufferers. Some BMS patients express both anxiety and depression or one or other [24–30]. Al Quran et al. [19], using a revised personality inventory, report that neuroticism and all its facets, which include anxiety, angry hostility, depression, self-consciousness, impulsiveness and vulnerability, were significantly elevated in BMS patients. Maina et al. [31] report that BMS is associated with a specific pattern of axis II comorbidity. BMS patients expressing significantly higher anxiety or depression scores and other personality disorders [27] often display high response rates to psychiatric or psychological interventions [30], antidepressants [32] and sedatives [15]. However, psychological dysfunction is common in patients with chronic pain and may be the result of the pain rather than its cause [33–35].

Metabolic causes of burning mouth symptoms embrace a wide variety of concurrent health conditions and chronic pain conditions, including headaches and pain in other locations (e.g. burning feet [36]). Patients with BMS often have high blood glucose levels, but no consistent or causal relationship has been documented [37]. The purported link between diabetes mellitus and BMS may be due to the occasional reports of glossodynia in known diabetic patients [38] and due to the fact that 50% of diabetic patients experience painful peripheral neuropathy (often 'burning feet'). Nutritional deficiencies (e.g. vitamins B_1, B_2 and B_6, zinc) are other findings that are not consistently supported by the literature [12]. A recent report suggests that hypothyroidism may predispose

patients to secondary BMS with 10, 8 and 80% of a 50-patient cohort displaying reduced tri-iodothyronine/thyroxine levels, antithyroid antibodies and echographic thyroid cystic changes [18].

Hormonal changes are considered to be important factors in BMS because in studies approximately 90% of the women suffering from the syndrome were postmenopausal, with the greatest frequency of onset reported from 3 years before to 12 years after the menopause [39]. There is also evidence of a reduction of lingual mucosal oestrogen receptors within the lingual mucosa; however, there is little convincing evidence of the efficacy of hormone replacement therapy in postmenopausal women with the disorder [39].

Pharmacogenic Factors

Hugoson and Thorstensson [40] reported that 87% of patients presenting with BMS were on concurrent medication, 44% of which were psychotropic drugs. Case reports have linked burning mouth symptoms to the use of angiotensin-converting enzyme inhibitors [41, 42]. Once these medications were reduced or discontinued, oral burning was found to remit within several weeks.

Neurogenic Factors

Systemic factors associated with general peripheral neuropathy include the following causes:

- metabolic (diabetes mellitus);
- toxic (ethanol/cytostatins/highly active anti-retroviral therapy);
- immune (acute inflammatory demyelinating polyneuropathy, acute motor and sensory axonal neuropathy);
- infective [human immunodeficiency virus (HIV)];
- hereditary (hereditary sensory and autonomic neuropathies type 1);
- a disorder of autonomic innervation and of oral blood flow [43];
- a sensory dysfunction associated with a small- and/or large-fibre sensory neuropathy [44];
- a disruption in sensory pathways driven by changes in endocrine status at menopause [37];
- a disruption of central sensory and modulatory pathways, including the spinal trigeminal nucleus and the striatum [45, 46].

Recent studies have pointed to a dysfunction of sensation as a possible cause of BMS. They have demonstrated significant alterations in chemosensory and heat pain tolerance [11, 47] as well as elevated sensory and pain thresholds to argon laser stimulation [48] in BMS patients as compared to control subjects. A recent investigation reports thin-fibre dysfunction in 35 (76%) of 46 BMS patients when tested using quantitative sensory tests and blink reflex [44].

Small-fibre sensory neuropathies predominantly occur in diabetic patients and present as 'burning feet'. Recent advances in understanding the aetiology, assessment and management of small-fibre neuropathies include the suggestion that BMS may be a peripheral sensory small-fibre neuropathy [49–51]. This is substantiated by a report that the total number of epithelial nerve fibres and the innervation density within the fungiform papillae and connective tissue was significantly reduced in BMS patients (n = 12) compared with controls (n = 9) in association with axonal degeneration [Renton et al., unpubl. work].

Current Hypotheses of Neuropathic Pain

Central sensitization and peripheral increased excitability in nociceptors play a role in neuropathic pain. Markers of small-fibre neuropathies include ion channels that are implicated in causation of chronic neuropathic pain states in diabetic and HIV neuropathies. Voltage-gated sodium channels also play key roles in the pathophysiology of pain and have been investigated in recent studies in pain mechanisms [52]. The distribution and pathophysiology of these channels, particularly NaV 1.8, have been the focus of research in pain mechanisms [53]. Recently, antisense treatment blocking this channel reportedly reduced neuropathic pain, which further supports the role of this channel in neuropathic pain. We have described the temporal and spatial distribution of NaV 1.8 in human sensory neurones [54]; the channels were decreased acutely in sensory cell bodies, after spinal cord root avulsion, but accumulated in fibres proximal to the site of injury in brachial plexus trunks and in neuromas. We have also reported that within the trigeminal system transient receptor potential vanilloid type 1 (TRPV1) and NaV 1.8 are expressed in the dental pulp and lingual nerve [55] (see the chapter by Khan and Hargreaves, pp 75–90).

Several high-profile studies of patients with neuropathic pain have shown that transmembrane ligand-activated ion channels (TRPV) are up-regulated in skin or mucosa during hypersensitive states and that sodium channels are up-regulated in skin associated with inflammatory conditions and with neuropathic pain subsequent to peripheral nerve injury in animal models. TRPV up-regulation is associated with rectal hypersensitivity [56], inflammation of the bowel [57], vulvodynia [58] and overactive bladder [59]. The increased receptor expression of the anal tissues correlates with increased thermal sensitivity as measured clinically before harvesting the tissue biopsies [56]. The increase in expression of receptors may infer increased activity. Another TRPV receptor (TRPM8), which responds to cool stimuli solely, may also be related to neuropathic pain. TRPM8 has been reported to be colocalized with TRPV1- and calcitonin-gene-related-peptide-positive fibres in the lingual nerve sensory fibres,

supplying the cold and menthol receptors of the tongue in Wistar rats, within the trigeminal ganglion, but not within the fungiform or filiform taste buds [60]. The TRPV receptors are also responsive to temperature changes and pain. In order to clinically assess the functionality of these receptors, thermal sensory thresholds were established. Using quantitative sensory testing with previously established methods [61], it would be expected that the thermal thresholds would correlate with the expression of TRPV1 and TRPM8 ion channels, as seen in rectal hypersensitivity [56] and diabetic neuropathy. These phenomena have recently been explored in the human mucosa in BMS. We have identified significant neuronal fibre degeneration within the lingual mucosa with significant up-regulation of TRPV1, nerve growth factor and NaV 1.8 levels in association with BMS. Interestingly, the increased TRPV1 immunoreactivity in the BMS lingual mucosa correlated strongly with patient-reported pain [Renton et al., unpubl. work].

There is a possibility that inherited genetic differences among individuals play an important role in susceptibility to the development and severity of pain. In mice, researchers have clearly demonstrated the major role that genetic differences among inbred strains play for several animal models of pain [62, 63]. In man, polymorphisms in the catechol-O-methyltransferase gene have been reported to be associated with differences in regional μ-opioid system response to pain [64]. Catechol-O-methyltransferase polymorphisms may also influence thermal experimental pain relative to psychological, gender and ethnic parameters [65] (see also the chapter by Stohler, pp 236–247).

Clinical Features

Symptoms

Many patients present with a chronic history and, in some, onset is sudden [47]. Around two thirds of patients cannot relate the onset of their symptoms to any factors, while others will relate it to either dental treatment or some other illness, such as upper respiratory tract infection [4, 11]. Significant life events may correlate with the onset of symptoms [10], but not all studies have found this [66] and Bogetto et al. [67] have suggested that their severity is more important. Using controls, Bogetto et al. [67] found that 17% of BMS patients had at least one severe life event compared with 9% in controls. The area affected in all patients is the tongue, followed by the lips as the next most common site. The symptoms may be present continuously or intermittently, and there does not appear to be any pattern. Not all patients consider the burning sensation to be a pain and so the words they use from the McGill Pain Questionnaire are very different from toothache. The words

chosen most frequently are 'burning' (85–65%), 'tender' (50%), 'annoying' (50%) and 'tiring' (37–34%) [14, 68].

Most studies have found that 50% of patients will have subjective oral dryness as a second feature [11, 14, 67, 69]. This could, however, be related to factors such as drugs, systemic diseases and psychological factors. Alteration in their perception of taste or a persistent altered taste (dysgeusia) or even a combination of both [22, 70] is often reported, and in some patients eating relieves it [8]. Svensson and Kaaber [14] compared denture-wearing BMS patients with controls; these researchers found that compared with controls BMS patients were less likely to wear dentures, and they had a decreased tongue space, an incorrect occlusal plane and a reduced vertical dimension.

Subjective reports of altered sensation must be noted, including paraesthesia, anaesthesia or dysaesthesia (spontaneous or evoked mechanical or thermal allodynia, hyperalgesia). Other associated features that have been reported include changes in sleep habits, mood and eating as well as decreased ability to socialize [22]. Patients with BMS have been the subject of considerable investigations in terms of psychiatric morbidity as detailed above. Eli et al. [71] have shown that BMS patients score significantly higher on scales of somatization, obsession-compulsion, personal sensitivity, depression, anxiety, hostility, phobic anxiety and psychoticism when compared to controls. They also found that BMS patients had a greater tendency to have had psychological treatment as compared to controls. Others have also reported a higher percentage of patients with depression, anxiety or mood changes [67, 72, 73]. However, Danhauer et al. [74] showed similar psychological features in patients with burning mouth due to other causes as BMS patients, so it could be that these are reactions to a chronic pain condition. Quality of life as measured on 14 questions using a Likert type format showed no difference between BMS and controls [71].

Signs

In BMS, no oral mucosal changes will be detected. However, a careful examination is essential to look for other causes of burning mouth. A dry mouth may be detected in some patients as well as evidence of parafunctional habits. Table 1 summarizes the clinical features.

Assessment and Investigations

A clinician's assessment of any patient presenting with pain will involve taking a detailed social, medical and pain history. Evaluation of the pain history, presenting symptoms (covered earlier in this chapter) and clinical examination revealing a lack of mucosal disease will probably heavily influence the

Table 1. Clinical features of BMS

Site and radiation	Tongue most common, but will also involve lips, cheeks, gingivae; all symptoms remain intra-oral
Character	Discomfort or pain; words used include 'burning', 'smarting', 'tender' and 'annoying'
Duration	Mean time to development 3 years, builds up gradually
Periodicity	Continuous or intermittent and may be worse in the evening
Severity	Ranges from mild to moderate
Relieving factors	Sleep, cold foods, distraction
Provoking factors	Tension, fatigue
Associated factors	Dryness, taste and/or mood changes, tongue thrusting
Examination	No gross changes, maybe some dryness

experienced clinician towards a diagnosis of BMS. This section specifically aims to address how BMS patients have been assessed in previous studies and to make some recommendations regarding the future routine clinical assessment.

Pain Assessment

All groups with oral mucosal pain should be asked to report the degree of baseline pain using a visual analogue scale (100 mm) at rest. Reactions to mechanical and thermal stimuli as well as taste can also be assessed using specific stimulants, and the resultant pains can be recorded.

Psychometric Assessment

Psychogenic factors have been consistently implicated in the aetiology of BMS [21] with a reported incidence of over 50% of psychological disorders within BMS patients [24]. As with any chronic pain, the patient will have consequential psychological changes (anxiety, depression, avoidance, stress). If BMS is proven to be a true neuropathy, then the reports on the psychogenic aetiology may be misguided. Several psychometric tools have been applied to BMS patients (Hospital Anxiety Depression Score, Personality Traits [24, 27–30] and Multiphasic Personality Inventory [16, 19, 31]).

Neurological Assessment

Clinical evidence of a peripheral sensory nerve lesion include hypoaesthesia assessed using a mechanosensory stimulus, e.g. von Frey fibres, thus identifying the neuropathic area (one must establish whether the area concords with neural dermatome boundaries in order to identify which nerve branch is affected). Neurophysiological tests undertaken by specialists confirm the loss of reflexes which may objectively confirm the loss of sensory afferent or motor

efferent pathways (blink reflex [44], jaw-opening reflex [75, 76]). Nerve conduction tests can also confirm the interruption of the sensory evoked potentials.

Modality Testing to Assess the Function of Specific Types of Neuronal Fibre Groups

All Fibres

Local analgesic blocks will elicit if the pain is of a peripheral source [77].

Large Myelinated Fibres

Mechanosensory afferents are Aβ fibres, so brush-evoked pain or mechanical allodynia can be elicited with oral mucosal pain using stimulation with a brush stroke (Sable 8 brush 2 cm across the tongue). The patients are asked to report the degree of pain using a visual analogue scale (100 mm). A clinical study of nerve injury pain has shown that in the presence of mechanical allodynia, a ratio between electrical pain and detection thresholds of less than 2.0 may indicate altered central nervous system processing of A fibre input [78]. This phenomenon may be an indication of altered central pain modulation and central sensitization. This phenomenon may be applicable to some BMS patients. Perception, mechanical detection threshold, 2-point discrimination test and thermal detection thresholds were similar in BMS patients and healthy volunteers [11, 27].

Small-Diameter Fibres

Aδ fibres respond to cooling or pain stimuli, while C fibres respond to warming and pain stimuli. Quantitative sensory testing involves the evaluation of thermal thresholds (Thermal Sensory Analyser TSA 2; Medoc, Israel) equipped with a hand-held probe (thermodes ranging from 5 mm × 5 mm to 6 cm × 3 cm in size). Testing begins with the measurement of warming and cooling sensory thresholds (fig. 1) using an adaptation temperature of 32°C and a temperature rate change of 1°C/s according to the method of limits [79].

Cold and heat pain thresholds can be similarly measured and suprapain thresholds enable the assessment of hyperpathia seen in a high proportion of BMS patients who display mechanosensory hyperalgesia [Renton et al., unpubl. work].

Thermal detection thresholds have been reported to be similar in BMS patients and healthy volunteers [11, 27]. However, using thermal discs thermal pain tolerance was significantly lower in BMS patients [47] suggesting faulty recruitment of pain-modulatory pathways. Pain and detection thresholds to argon laser stimuli were significantly higher and ratios between pain and sensory thresholds significantly lower in patients with BMS in all examined oral regions [14], suggesting a perceptual deficit unrelated to the painful site only.

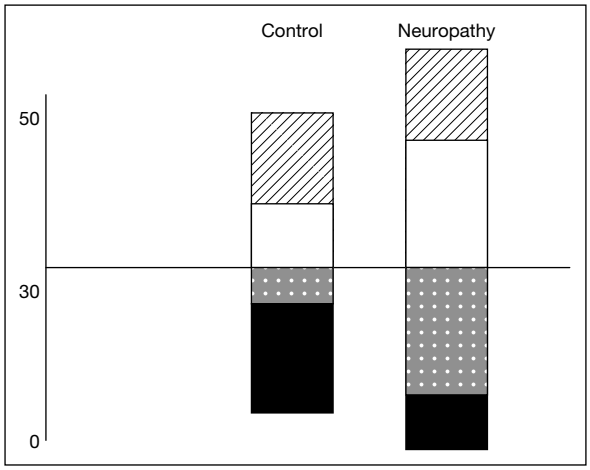

Fig. 1. The baseline temperature at 32°C warm sensory threshold (□) and cool sensory threshold (▩) as well as heat pain threshold (▨) and cold pain threshold (■) in controls and patients with neuropathy.

The sweet taste detection threshold is higher in BMS patients [70] demonstrating an altered taste sensation. Application of Dyclonin (a local anaesthetic solution) to the tongue of BMS patients reduced phantom dysgeusia but did not reduce the burning sensation; moreover, in 40% of the cases the pain was aggravated [80].

Taste

There are several methods to assess chorda tympani function, one of which is the electrogustatory test. The test is well established and is a reliable clinical tool [81], despite the fact that the stimulating mechanisms of electrical taste are multifaceted. In addition to the direct nerve fibre activation by the electrical stimulus, pH changes employed by the electrical current may contribute to the taste sensation. The electrical current causes hydrogen ion discharge from the anode leading to pH reduction in the surrounding saliva; the acidic saliva activates ionic receptor triggering inducing perception of sour taste [82]. However, electrical stimulation incorporates unique properties that are very useful for sensory assessment. Unlike the other methods which naturally stimulate nerve receptors, electrical stimuli may bypass the receptor to stimulate the axon of the primary afferent. Due to this property, electrical stimuli are not affected by changes in receptor sensitivity such as sensitization, suppression or fatigue. In sites other than the tongue, altered electrical sensitivity alone indicates a postreceptor process, while altered natural stimuli cannot distinguish between a

receptor and postreceptor processes. In previous studies, in order to minimize electrical detection threshold intersubject variability, the results were expressed as side-to-side ratio for each tested area [83, 84]. However, as the anterior two thirds of the tongue are innervated by 2 sensory nerves (chorda tympani for taste and lingual for other modalities), electrical taste and itch (tingling) detection ratio may be a reliable and repeatable score.

Biopsy

Skin biopsies are a routine clinical tool for the neurologist to confirm peripheral neuropathy in HIV and diabetes-related peripheral neuropathies. Changes in diabetic peripheral neuronal supply can be seen early on, prior to the onset of burning feet with degeneration of epithelial neurons and increased expression of pain-related neural receptor [85]. The degeneration of the subepithelial fibres may be a precursor to developing neuropathic pain. Quantification of epithelial nerve fibres and coexpression of ion channels and neuropeptides can be undertaken using immunohistochemical studies that utilize image analysis or Western blotting assays to measure the expression of the specific pain receptors. Both pain-related receptor TRPV1 and sodium channel NaV 1.8 [85] are associated with HIV and diabetic neuropathic pain; they are also up-regulated in the lingual mucosa in BMS patients [Renton et al., unpubl. work].

Biopsy looking at oestrogen receptors [86] has been recommended as a tool to determine which patients had diminished oestrogen receptors within the lingual mucosa so that they could be targeted for hormone replacement therapy.

Management

BMS needs to be managed holistically using patient-centred care and including medical and psychosocial methods simultaneously. A Cochrane systematic review [87] and the paper in *Clinical Evidence* [9] on interventions in BMS are regularly updated. Treatments can be divided into 3 main categories: systemic, topical and behavioural. These are summarized in table 2.

Medical Management

Hormonal Replacement Therapy

There have been a variety of trials using hormone replacement therapy either systemically or topically, but they are all poor-quality non-randomized intervention studies with no clear diagnostic criteria or outcome measures. One randomized controlled trial (RCT) [98] compared in 56 postmenopausal

Table 2. Randomized controlled trials for patients with BMS

Drug/treatment duration	Therapy/number of patients	Efficacy	Side-effects/adverse	Comments	Authors
CBT/12–15 weeks	12–15 sessions of CBT versus attention placebo/30 patients	At 6 months, 27% improvement in active group, pain-free	None	VAS was not validated, no details whether groups were comparable	Bergdahl et al. [88]
Antidepressant/ 8 weeks	Trazodone 200 mg versus placebo/37 patients	Both groups show the same improvement	Dizziness in 11, drowsiness in 9 patients	RCT, good outcome measures	Tammiala-Salonen and Forssell [89]
Antidepressant/ 6 weeks	Clomipramine 75–100 mg versus mianserin 30–60 mg versus placebo/BMS 77 patients, total facial pain 253 patients	No improvement	Drop-outs due to side-effects	No blinding, lack of follow-up, other types of pain included, impossible to ascertain which patients had BMS; large drop-out rate	Loldrup et al. [90]
Antidepressant/ 8 weeks	Amisulpride 50 mg, 27 patients; paroxetine 20 mg, 26 patients; sertraline 50 mg, 23 patients	Mean score reduction: 4.4 with sertraline versus 3.7 with paroxetine versus 4.0 with amisulpride	Nausea, sedation and dryness, 3 withdrew	Single blinding, no placebo; many patients had a concurrent psychiatric diagnosis	Maina et al. [91]

Table 2. (continued)

Drug/treatment duration	Therapy/number of patients	Efficacy	Side-effects/adverse	Comments	Authors
Systemic capsaicin/ 30 days	Capsaicin 0.25% versus placebo/50 patients	Capsaicin group: score 5.84 ± 1.17 compared to placebo group: score 6.24 ± 0.96 on the VAS	8 patients with gastro-intestinal side-effects	Small study; pseudorandomization	Petruzzi et al. [92]
Vitamin replacement/ 30 days	α-Lipoic acid 600 mg versus placebo/42 patients	Slight improvement 16/21 active versus 3/21 placebo	None mentioned	Assessment not blinded	Femiano et al. [93]
Vitamin replacement/ 8 weeks	α-Lipoic acid 600 mg for 2 months versus placebo/60 patients	29/30 (97%) improved in the active, 12/30 (40%) improved in the placebo group	No drop-out	Not blinded, subjective outcomes, randomization (?)	Femiano and Scully [94]
Vitamin replacement/ 8.5 weeks	α-Lipoic acid 600 mg versus bethanechol 15 mg versus biotene versus placebo/ 80 patients	α-Lipoic acid group: 90% improved; biotene group: 0% improved; bethanechol group: 10% improved; placebo group: 0% improved	Nil drop-out; group 1: increased salivation, nausea, decreased blood pressure; group 3: heartburn	Not sure if groups comparable, randomization(?), no blinding, many participants used anxiolytics	Femiano [95]

Topical clonazepam/ 14 days	Clonazepam 1 mg sucked slowly for 3 min t.i.d./ 24 patients	Decrease in pain scores of 2.4 ± 0.6 in the clonazepam group and of 0.6 ± 0.4 in the placebo group on a VAS 0–10	Drowsiness (4/24), increased burning sensation (2/24), dry mouth (1/24) and euphoria (1/24); 2 withdrew from treatment group due to side-effects	RCT, blinded effect was evaluated at 6 months in 16 patients who reported an improvement; 7 participants had continued improvement	Gremeau-Richard et al. [96]
Topical analgesic/ 4 weeks	Benzydamine mouth rinse versus placebo versus no treatment/30 patients	No improvement in all 3 groups	Nil	Small RCT, good outcome measures, last group not blinded	Sardella et al. [97]

CBT = Cognitive-behavioural therapy; VAS = visual analogue scale.

women oral tibolone 2.5 mg daily versus oryzanol (30 mg 3 times/day) plus vitamin E (100 mg 3 times/day). Oryzanol is a product mainly derived from rice bran oil and is used as a food supplement. It was found that tibolone significantly improved symptoms compared with oryzanol plus vitamin E at 3 and 6 months. The study had several flaws, however: it did not specify the method of randomization; it was not blinded; the scale used for assessing improvement of symptoms was not validated, and there were important differences between the groups at baseline. Therefore, the results need to be interpreted with caution.

Vitamin Replacements

There have been several trials reporting the use of α-lipoic acid. All 3 RCTs evaluated outcomes on a 5-point scale (symptoms 'worsening', 'unchanged', 'slight improvement', 'decided improvement' or 'resolution') [93–95]. α-Lipoic acid (600 mg/day) was compared with placebo in 2 trials, whereas the third RCT (80 people) compared α-lipoic acid (200 mg 3 times/day), lactoperoxidase mouth rinse (5–6 times/day), bethanechol (5 mg 3 times/day) and placebo. Only α-lipoic acid increased the proportion of people reporting improvement on the symptom scale. Mild side-effects were reported by 4 people in the α-lipoic acid group, i.e. heartburn, which settled with ranitidine. Four people taking bethanechol experienced adverse events, including nausea, dizziness, cold perspiration or abdominal pain. All 3 trials have design faults, e.g. lack of blinding, no details on randomization and subjective outcome measures. They all originate from the same centre at overlapping time periods. The results need to be interpreted with care.

Antidepressants

Antidepressants are used, but often BMS patients have not been analysed separately from other facial pain patients so their individual outcomes are not known.

Clomipramine/Mianserin

One RCT comprising 253 people with chronic idiopathic pain syndrome included 77 people with BMS. It compared clomipramine, mianserin and placebo [90]. Since it was not possible to determine the outcomes on the BMS separately, the investigation does not provide sufficient evidence to determine the role of antidepressants in treating BMS.

Trazodone

A double-blind well-conducted RCT in 37 women compared trazodone (200 mg daily) with placebo for 8 weeks [89]. No significant differences in pain or related symptoms were found between trazodone and placebo. Withdrawal from the trial was high (7/18; 39%) due to factors such as dizziness and drowsiness.

Selective Serotonin Reuptake Inhibitors versus Amisulpride

A small RCT (76 individuals), using daily doses of sertraline (50 mg), paroxetine (20 mg) and amisulpride (50 mg) for 8 weeks found a similar reduction in pain scores in all 3 groups [91]. No serious adverse effects in any treatment group were reported. The trial did not include a placebo group, there was single blinding only, and many of the patients had a psychiatric diagnosis. Therefore the results do not provide sufficient evidence for their use.

Capsaicin

Capsaicin is a naturally occurring alkaloid found in red chilli peppers. It has been used as a topical agent (0.025% gel) for postherpetic neuralgia, and there are anecdotal reports of its use in patients with burning mouth symptoms. Topically applied in the mouth, its use is reduced by its unpleasant taste and limited efficacy. Recently, results from a small RCT (50 patients) were reported which compared systemic 0.25% capsaicin taken 3 times a day with placebo over 4 weeks. A significant reduction in mean visual analogue scale scores (capsaicin group: 5.84 ± 1.17; placebo group: 6.24 ± 0.96) was found, although the response was variable [92]. Not surprisingly, 8 patients reported gastric pain with oral capsaicin. This adverse effect appeared to be related to the duration of use and would be likely to limit adherence if used for periods greater than the 1-month period employed in this trial. The RCT has design weakness including pseudorandomization, small sample size and short duration.

Topical Clonazepam

One small 14-day RCT (48 people) compared topical clonazepam (1 mg sucked 3 times a day, held in the mouth for 3 min then expectorated) with placebo. There was a subsequent open follow-up at 6 months [96]. One third of the subjects used occasional hypnotics, usually benzodiazepines. There was a decrease in pain scores in the clonazepam group, but the response was very variable. In the 16 patients who continued it in an open follow-up, 7 continued to benefit.

Within the RCT, reported side-effects were not significantly more frequent in the treatment group when compared to the control group, but drowsiness (4/24), increased burning sensation (2/24), dry mouth (1/24) and euphoria (1/24) were reported. Two subjects withdrew from the treatment group because of side-effects. Five patients using topical clonazepam were assessed for systemic absorption after 14 days of treatment. Whilst the blood concentration of clonazepam was not within therapeutic ranges, there was evidence of systemic absorption at up to 8 mg/l. The trial was well conducted but of short duration. The use of clonazepam in the management of BMS is limited.

Benzydamine Hydrochloride

In a small RCT of 30 patients, benzydamine hydrochloride oral rinse (15 ml of 0.15% for 1 min 3 times daily for 4 weeks) was compared with placebo and no treatment [97]. No significant difference in symptoms was found among groups at 4 weeks. However, the trial was too small to detect a clinically important difference. Furthermore, it was incompletely blinded because the third group received no treatment.

Saliva Substitutes

Patients who complain of dry mouth may be offered a variety of saliva substitutes which have not been evaluated in RCTs.

Behavioural Management

There is only one small RCT of 30 BMS patients in whom cognitive-behavioural therapy (12–15 sessions of 1 h/week) was compared to a control group who received similar attention, but without the cognitive-behavioural therapy sessions [88]. It was found that cognitive-behavioural therapy significantly reduced the intensity of symptoms at 6 months; no adverse effects were reported. The trial was small and individual characteristics of the two groups were not described; therefore, the groups may not have been comparable. The visual analogue scale for assessing oral burning was not validated. There is limited evidence for its effectiveness.

All patients can be reassured that the symptom is not a sign of a more sinister disease. A survey carried out in the Netherlands where there is a support group for patients with burning mouths indicates that 88% wanted more information from their health care workers. Up to 57% said they were poorly informed by either dentist or physician [99]. Patient education will help patients accept BMS as a long-term condition that has to be managed in a variety of ways using a biopsychosocial approach.

References

1 Tourne LP, Fricton JR: Burning mouth syndrome: critical review and proposed clinical management. Oral Surg Oral Med Oral Pathol 1992;74:158–167.

2 Bergdahl J, Anneroth G: Burning mouth syndrome: literature review and model for research and management. J Oral Pathol Med 1993;22:433–438.

3 Zakrzewska JM, Hamlyn PJ: Facial pain; in Crombie IKCPR, Linton SJ, LeResche L, Von Korff M (eds): Epidemiology of Pain. Seattle, IASP Press, 1999, pp 171–202.

4 Tammiala-Salonen T, Hiidenkari T, Parvinen T: Burning mouth in a Finnish adult population. Community Dent Oral Epidemiol 1993;21:67–71.

5 Femiano F: Indagine statistica delle patologie afferenti in cinque anni di attivita presso il reparto di patologia orale II università di Napoli. Minerva Stomatol 2002;51:73–78.

6 Grushka M, Katz RL, Sessle BJ: Spontaneous remission in burning mouth syndrome (abstract). J Dent Res 1986;274:abstr 1341.

7 Sardella A, Lodi G, Demarosi F, Bez C, Cassano S, Carrassi A: Burning mouth syndrome: a retrospective study investigating spontaneous remission and response to treatments. Oral Dis 2006;12:152–155.
8 Bergdahl M, Bergdahl J: Burning mouth syndrome: prevalence and associated factors. J Oral Pathol Med 1999;28:350–354.
9 Buchanan AG, Zakrzewska JM: Burning mouth syndrome; in Young C (ed): Clinical Evidence Concise. London, BMJ Publishing Group, 2006, pp 541–542.
10 Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA: Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 2003;14:275–291.
11 Grushka M: Clinical features of burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:30–36.
12 Ship JA, Grushka M, Lipton JA, Mott AE, Sessle BJ, Dionne RA: Burning mouth syndrome: an update. J Am Dent Assoc 1995;126:842–853.
13 Marks R, Scarff CE, Yap LM, Verlinden V, Jolley D, Campbell J: Fungiform papillary glossitis: atopic disease in the mouth? Br J Dermatol 2005;153:740–745.
14 Svensson P, Kaaber S: General health factors and denture function in patients with BMS and matched control subjects. J Oral Rehabil 1995;22:887–895.
15 Levy LM, Henkin RI: Human taste phantoms can be related to specific regional areas of decreased brain γ-aminobutyric acid (GABA) by magnetic resonance spectroscopy (MRS) (abstract). Paper presented at Biomedicine '98: Medical Research from Bench to Bedside, Washington, DC, May 1–3, 1998. J Invest Med 1998;46:219A.
16 Granot M , Nagler RM: Association between regional idiopathic neuropathy and salivary involvement as the possible mechanism for oral sensory complaints. J Pain 2005;6:581–587.
17 Bartoshuk LM, Duffy VB, Lucchina LA, Prutkin J, Fast K: PROP (6-n-propylthiouracil) supertasters and the saltiness of NaCl. Ann NY Acad Sci 1998;855:793–796.
18 Femiano F: Damage to taste system and oral pain: burning mouth syndrome. Minerva Stomatol 2004;53:471–478.
19 Al Quran FA: Psychological profile in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:339–344.
20 Whitehead MC, Beeman CS, Kinsella BA: Distribution of taste and general sensory nerve endings in fungiform papillae of the hamster. Am J Anat 1985;173:185–201.
21 Grushka M, Kawalec J, Epstein JB: Burning mouth syndrome: evolving concepts. Oral Maxillofac Surg Clin North Am 2000;12:287–295.
22 Bartoshuk LM, Grushka M, Duffy VB, Fast L, Lucchina L, Prutkin J, et al: Burning mouth syndrome: damage to CN VII and pain phantoms in CN V (abstract). Chem Senses 1999;24:609.
23 Triantos D, Kanakis P: Stomatodynia (burning mouth) as a complication of enalapril therapy. Oral Dis 2004;10:244–245.
24 Browning S, Hislop S, Scully C, Shirlaw P: The association between burning mouth syndrome and psychosocial disorders. Oral Surg Oral Med Oral Pathol 1987;64:171–174.
25 Carlson CR, Miller CS, Reid KI: Psychosocial profiles of patients with burning mouth syndrome. J Orofac Pain 2000;14:59–64.
26 Lamey PJ, Lamb AB: The usefulness of the HAD scale in assessing anxiety and depression in patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1989;67:390–392.
27 Lamey PJ, Freeman R, Eddie SA, Pankhurst C, Rees T: Vulnerability and presenting symptoms in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:48–54.
28 Paterson AJ, Lamb AB, Clifford TJ, Lamey PJ: Burning mouth syndrome: the relationship between the HAD scale and parafunctional habits. J Oral Pathol Med 1995;24:289–292.
29 Zilli C, Brooke RI, Lau CL, Merskey H: Screening for psychiatric illness in patients with oral dysesthesia by means of the General Health Questionnaire – twenty-eight item version (GHQ-28) and the Irritability, Depression and Anxiety Scale (IDA). Oral Surg Oral Med Oral Pathol 1989;67:384–389.
30 Rojo L, Silvestre FJ, Bagan JV, De Vicente T: Psychiatric morbidity in burning mouth syndrome: psychiatric interview versus depression and anxiety scales. Oral Surg Oral Med Oral Pathol 1993;75:308–311.
31 Maina G, Albert U, Gandolfo S, Vitalucci A, Bogetto F: Personality disorders in patients with burning mouth syndrome. J Pers Disord 2005;19:84–93.

32 Gorsky M, Silverman S Jr, Chinn H: Clinical characteristics and management outcome in the burning mouth syndrome: an open study of 130 patients. Oral Surg Oral Med Oral Pathol 1991;72: 192–195.
33 Brody HA, Nesbitt WR: Psychosomatic oral problems. J Oral Med 1967;22:43–46.
34 Popper F: Psychogenic aspects of the burning mouth. J Dent Assoc S Afr 1968;23:357–358.
35 Grushka M, Epstein JB, Gorsky M: Burning mouth syndrome. Am Fam Physician 2002;65: 615–620, 622.
36 Grushka M, Ching V: Preliminary exploration of burning mouth and burning feet: is there a common etiology? Pain Res Manag 2005;10:166–167.
37 Basker RM, Sturdee DW, Davenport JC: Patients with burning mouths: a clinical investigation of causative factors, including the climacteric and diabetes. Br Dent J 1978;145:9–16.
38 Carrington J, Getter L, Brown RS: Diabetic neuropathy masquerading as glossodynia. J Am Dent Assoc 2001;132:1549–1551.
39 Forabosco A, Criscuolo M, Coukos G, Uccelli E, Weinstein R, Spinato S, et al: Efficacy of hormone replacement therapy in postmenopausal women with oral discomfort. Oral Surg Oral Med Oral Pathol 1992;73:570–574.
40 Hugoson A, Thorstensson B: Vitamin B status and response to replacement therapy in patients with burning mouth syndrome. Acta Odontol Scand 1991;49:367–375.
41 Drucker CR, Johnson TM: Captopril glossopyrosis. Arch Dermatol 1989;125:1437–1438.
42 Savino LB, Haushalter NM: Lisinopril-induced 'scalded mouth syndrome'. Ann Pharmacother 1992;26:1381–1382.
43 Heckmann SM, Heckmann JG, HiIz MJ, Popp M, Marthol H, Neundorfer B, Hummel T: Oral mucosal blood flow in patients with burning mouth syndrome. Pain 2001;90:281–286.
44 Forssell H, Jaaskelainen S, Tenovuo O, Hinkka S: Sensory dysfunction in burning mouth syndrome. Pain 2002;99:41–47.
45 Hagelberg N, Forssell H, Rinne JO, Scheinin H, Taiminen T, Aalto S, Luutonen S, Nagren K, Jaaskelainen S: Striatal dopamine D_1 and D_2 receptors in burning mouth syndrome. Pain 2003;101: 149–154.
46 Eguía Del Valle A, Aguirre-Urizar JM, Martinez-Conde R, Echebarria-Goikouria MA, Sagasta-Pujana O: Burning mouth syndrome in the Basque Country: a preliminary study of 30 cases. Med Oral 2003;8:84–90.
47 Grushka M, Sessle BJ, Howley TP: Psychophysical assessment of tactile pain and thermal sensory functions in burning mouth syndrome. Pain 1987;28:169–184.
48 Svensson P, Bjerring P, Arendt-Nielson L, Kaaber S: Sensory and pain thresholds to orofacial argon laser stimulation in patients with chronic burning mouth syndrome. Clin J Pain 1993;9: 207–215.
49 Lauritano D, Spadari F, Formaglio F, Zambellini Artini M, Salvato A: Aspetti eziopatogenetici, clinico-diagnostici e terapeutici della sindrome della bocca bruciante: protocolli di ricerca e cura su un gruppo di pazienti. Minerva Stomatol 1998;47:239–251.
50 Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, Padovani A, Sapelli P: Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 2005;115:332–337.
51 Lauria G: Small fibre neuropathies. Curr Opin Neurol 2005;18:591–597.
52 Waxman SG: The molecular pathophysiology of pain: abnormal expression of sodium channel genes and its contributions to hyperexcitability of primary sensory neurons. Pain 1999;(suppl 6): S133–140.
53 Yiangou Y, Facer P, Sinicropi DV, Boucher TJ, Bennett DL, McMahon SB, Anand P: Molecular forms of NGF in human and rat neuropathic tissues: decreased NGF precursor-like immunoreactivity in human diabetic skin. J Peripher Nerv Syst 2002;7:190–197.
54 Coward K, Plumpton C, Facer P, Birch R, Carlstedt T, Tate S, Bountra C, Anand P: Immunolocalization of SNS/PN3 and NaV1.9 sodium channels in human pain states. Pain 2000;85:41–50.
55 Renton T, Yiangou Y, Plumpton C, Tate S, Bountra C, Anand P: Sodium channel NaV1.8 immunoreactivity in painful human dental pulp. BMC Oral Health 2005;5:5.
56 Chan CLH, Facer P, Davis JB, Smith GD, Egerton J, Bountra C, Williams NS, Anand P: Sensory fibres expressing capsaicin receptor TRPVR1 in patients with rectal hypersensitivity and faecal urgency. Lancet 2003;361:385–391.

57 Yiangou Y, Facer P, Dyer NH, Chan CL, Knowles C, Williams NS, Anand P: Vanilloid receptor 1 immunoreactivity in inflamed human bowel. Lancet 2001;357:1338–1339.
58 Tympanidis P, Casula MA, Yiangou Y, Terenghi G, Dowd P, Anand P: Increased vanilloid receptor VR1 innervation in vulvodynia. Eur J Pain 2004,8:129–133.
59 Avelino A, Cruz F: Peptide immunoreactivity and ultrastructure of rat urinary bladder nerve fibers after topical desensitization by capsaicin or resiniferatoxin. Auton Neurosci 2000;86: 37–46.
60 Abe J, Hosokawa H, Okazawa M, Kandachi M, Sawada Y, Yamanaka K, Matsumura K, Kobayashi S: RPM8 protein localization in trigeminal ganglion and taste papillae. Brain Res Mol Brain Res 2005;136:91–98.
61 Renton T, Yiangou Y, McGurk M, Plumpton C, Tate S, Bountra C, Anand P: Presence of VR1 and P2X3 sodium channels in tooth pulp. J Orofac Pain 2003;17:245–250.
62 Mogil JS: The genetic mediation of individual differences in sensitivity to pain and its inhibition. Proc Natl Acad Sci USA 1999;96:7744–7751.
63 Mogil JS, Ritchie J, Smith SB, Strasburg K, Kaplan L, Wallace MR, Romberg RR, Bijl H, Sarton EY, Fillingim RB, Dahan A: Melanocortin-1 receptor gene variants affect pain and μ-opioid analgesia in mice and humans. J Med Genet 2005;42:583–587.
64 Zubieta JK, Ketter TA, Bueller JA, Xu Y, Kilbourn MR, Young EA, Koeppe RA: Regulation of human affective responses by anterior cingulate and limbic μ-opioid neurotransmission. Arch Gen Psychiatry 2003;60:1145–1153.
65 Kim H, Neubert JK, San Miguel A, Xu K, Krishnaraju RK, Iadarola MJ, Goldman D, Dionne RA: Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. Pain 2004;109:488–496.
66 Eli I, Kleinhauz M, Baht R, Littner M: Antecedents of burning mouth syndrome (glossodynia) – recent life events vs psychopathologic aspects. J Dent Res 1994;73:567–572.
67 Bogetto F, Maina G, Ferro G, Carbone M, Gandolfo S: Psychiatric comorbidity in patients with burning mouth syndrome. Psychosom Med 1998;60:378–385.
68 Locker D, Grushka M: The impact of dental and facial pain. J Dent Res 1987;66:1414–1417.
69 Bergdahl BJ, Anneroth G, Anneroth I: Clinical study of patients with burning mouth. Scand J Dent Res 1994;102:299–305.
70 Grushka M, Sessle B: Taste dysfunction in burning mouth syndrome. Gerodontics 1988;4:256–258.
71 Grushka M, Sessle BJ, Miller R: Pain and personality profiles in burning mouth syndrome. Pain 1987;282:155–167.
72 Eli I, Baht R, Littner MM, Kleinhauz M: Detection of psychopathologic trends in glossodynia patients. Psychosom Med 1994;565:389–394.
73 Bergdahl J, Anneroth G, Perris H: Personality characteristics of patients with resistant burning mouth syndrome. Acta Odontol Scand 1995;53:7–11.
74 Danhauer SC, Miller CS, Rhodus NL, Carlson CR: Impact of criteria-based diagnosis of burning mouth syndrome on treatment outcome. J Orofac Pain 2002;16:305–311.
75 Renton T, Thexton A, Mcgurk M: New method for the objective evaluation of injury to the lingual nerve after operation on third molars. Br J Oral Maxillofac Surg 2005;43:238–245.
76 Renton T, Thexton A, McGurk M: Quantitative thermosensory testing of the lingual and inferior alveolar nerves in health and after iatrogenic injury. Br J Oral Surg 2003;41:36–42.
77 Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, Clark MR, Raja SN: Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. Anesthesiology 2000;92:691–698.
78 Sang CN, Max MB, Gracely RH: Stability and reliability of detection thresholds for human Aβ and Aδ sensory afferents determined by cutaneous electrical stimulation. J Pain Symptom Manag 2003;25:64–73.
79 Fruhstorfer H, Lindblom U, Schmidt WC: Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976;39:1071–1075.
80 Formaker BK, Frank ME: Taste function in patients with oral burning. Chem Senses 2000;25: 575–581.
81 Tomita H, Horikawa Y: Dissociated taste disorder. Auris Nasus Larynx 1986;13(suppl 1): S17–S23.

82 DeSimone JA, Lyall V, Heck GL, Phan TH, Alam RI, Feldman GM, Buch RM: A novel pharmacological probe links the amiloride-insensitive NaCl, KCl, and NH_4Cl chorda tympani taste responses. J Neurophysiol 2001;86:2638–2641.
83 Eliav E, Gracely RH, Nahlieli O, Benoliel R: Quantitative sensory testing in trigeminal nerve damage assessment. J Orofac Pain 2004;18:339–344.
84 Benoliel R, Sharav Y: Neuropathic orofacial pain. Compend Contin Educ Dent 1998;19: 1099–1102, 1104.
85 Anand P: Neurotrophic factors and their receptors in human sensory neuropathies. Prog Brain Res 2004;146:477–492.
86 Santoro V, Caputo G, Peluso F: Clinical and therapeutic experience in twenty eight patients with burning mouth syndrome. Minerva Stomatol 2005;54:489–496.
87 Zakrzewska JM, Forssell H, Glenny AM: Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev 2005;1:CD002779.
88 Bergdahl J, Anneroth G, Perris H: Cognitive therapy in the treatment of patients with resistant burning mouth syndrome: a controlled study. J Oral Pathol Med 1995;24:213–215.
89 Tammiala-Salonen T, Forssell H: Trazodone in burning mouth pain: a placebo-controlled, double-blind study. J Orofac Pain 1999;13:83–88.
90 Loldrup D, Langemark M, Hansen HJ, Olesen J, Bech P: Clomipramine and mianserin in chronic idiopathic pain syndrome: a placebo controlled study. Psychopharmacology (Berl) 1989;99:1–7.
91 Maina G, Vitalucci A, Gandolfo S, Bogetto F: Comparative efficacy of SSRIs and amisulpride in burning mouth syndrome: a single-blind study. J Clin Psychiatry 2002;63:38–43.
92 Petruzzi M, Lauritano D, De Benedittis M, Baldoni M, Serpico R: Systemic capsaicin for burning mouth syndrome: short-term results of a pilot study. J Oral Pathol Med 2004;33:111–114.
93 Femiano F, Gombos F, Scully C, Busciolano M, Luca PD: Burning mouth syndrome (BMS): controlled open trial of the efficacy of α-lipoic acid (thioctic acid) on symptomatology. Oral Dis 2000;6:274–277.
94 Femiano F, Scully C: Burning mouth syndrome (BMS): double blind controlled study of α-lipoic acid (thioctic acid) therapy. J Oral Pathol Med 2002;31:267–269.
95 Femiano F: Burning mouth syndrome (BMS): an open trial of comparative efficacy of α-lipoic acid (thioctic acid) with other therapies. Minerva Stomatol 2002;51:405–409.
96 Gremeau-Richard C, Woda A, Navez ML, et al: Topical clonazepam in stomatodynia: a randomised placebo-controlled study. Pain 2004;108:51–57.
97 Sardella A, Uglietti D, Demarosi F, Lodi G, Bez C, Carrassi A: Benzydamine hydrochloride oral rinses in management of burning mouth syndrome: a clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88:683–686.
98 Peng JY, Wu YF, Han WN: Clinical efficacy of burning mouth syndrome treated by livial. Hunan Yi Ke Da Xue Xue Bao (Bulletin of Hunan Medical University) 2001;26:157–158.
99 van der Ploeg HM, van der Wal N, Eijkman MA, van der Waal I: Psychological aspects of patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:664–668.

Joanna M. Zakrzewska, MD, FDSRCS (Eng)
Professor of Pain in Relation to Oral Medicine
Hon. Consultant Clinical and Diagnostic Oral Sciences
Institute of Dentistry
Barts and the London Queen Mary's School of Medicine and Dentistry
Turner Street, London E1 2AD (UK)
Tel. +44 20 7377 7053, Fax +44 20 7377 7627, E-Mail j.m.zakrzewska@qmul.ac.uk

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 187–208

Psychosocial Impact of Orofacial Pain

Samuel F. Dworkin

Seattle, Wash., USA

Abstract

The major objectives for the chapter are to provide psychosocial perspectives with regard to current knowledge on clinical presentation, psychological, behavioral and social factors underlying the presentation of dental and orofacial pain as well as an overview of the biobehavioral management of orofacial pain. Psychosocial aspects of pain and pain control are studied because emotional states, thought processes and behavior greatly influence how pain is experienced and, most critical of all, because understanding of the psychosocial aspects of pain experience expands possibilities for management of dental and orofacial pain to achieve the following objectives: (1) produce a more compliant and better-informed patient who can learn to accept dentistry without undue apprehension and be more compliant with treatment recommendations that may require prolonged patient cooperation and participation; (2) eliminate or minimize negative physiological and emotional states, especially depression, anxiety, fear and the anticipation of pain or harm too often associated with pending dental treatment or with chronic physical conditions in which pain is a predominant feature, and (3) introduce a wide variety of cognitive-behavioral methods which are available to assist the patient in self-management and enhanced self-control for both acute and chronic pain, with and without analgesic, sedative, anesthetic or mood-modifying medications.

Overview: The Psychosocial Perspective

It must be emphasized at the onset that the psychosocial perspectives and methods related to dental and orofacial pain are never offered as a substitute for the absolutely crucial need to consider simultaneously the biology of pain, including especially pathophysiological mechanisms and biomedical methods for managing orofacial pain. In this context, the model system invoked to understand orofacial pain is a biopsychosocial model [1], which clarifies how physical events in the body or in the environment often give rise to not readily predicted pain experiences and behaviors related to the patient's past pain

Table 1. Acute and chronic dental and orofacial pain: relationships among physical, environmental, psychological and psychosocial factors

Type of pain	Source of pain		Psychological and psychosocial factors		
	pathological/ endogenous	iatrogenic/ environmental	emotional states	cognitive processes	pain behaviors
Dental					
Acute pain (typically recent onset, brief, often consistent with physical findings)	Infection Inflammation Malignancy Often known etiology	Trauma Intraoperative Postoperative Often known etiology	Anxiety Panic Phobia	Anticipation and apprehension over threat or harm	Agitation ANS arousal Sleep problems
Orofacial					
Chronic pain (typically persistent, recurrent, often inconsistent with physical findings)	Neuropathic Musculoskeletal Soft tissue Malignancy Often unknown etiology	Postsurgical Postmedical treatment Often unknown etiology	Depression Anger	Negativism Hopelessness Worry	Isolation Avoidance Sleep problems Extensive health care use Medications abuse

ANS = Autonomic nervous system.

history, emotional status, social factors, gender, ethnicity and culture [2]. Such a biopsychosocial model, integrating biological processes, psychological status and psychosocial functioning forms the basis not only for all pain research and pain management, but also for all medical education in the USA and Canada as well as elsewhere around the world. The need for such a biopsychosocial perspective is immediately apparent when one closely examines the prevailing scientific definition of pain and pain-related terms.

The universally accepted scientific definition of pain is provided by the International Association for the Study of Pain (IASP):

> Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [3].

It is important to note that this definition is further amplified by the IASP specifically to insure clarity of concepts and terms used to define pain:

> Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage . . . [pain] is always subjective . . . but it is also always unpleasant . . . therefore also an emotional experience . . . even though we may well appreciate that pain most often has a proximate physical cause.

Introduction

In this chapter, we will consider the impact on people's lives resulting from the infinitely varied ways people perceive and evaluate or appraise pain and then how they behave in response to the dental and orofacial pain they are experiencing. Evidence-based biobehavioral approaches to the management of pain are presented which are intended to complement the probably better known biologically and medically based surgical and pharmacological pain treatments that are commonly associated with dental and orofacial pain management in dentistry. While psychosocial perspectives on both dental and orofacial pain are discussed, the greatest emphasis in this chapter will be on psychosocial considerations in chronic orofacial pain because of the greater psychosocial impact of chronic orofacial pain and because dentists generally seem to be less familiar with biobehavioral management methods for chronic orofacial pain management, compared to acute pain. Table 1 compares the important psychosocial differences between acute and chronic dental and orofacial pain.

The structures of the stomatognathic system are responsible for several life-sustaining physiological processes, including eating, breathing, swallowing and verbal as well as nonverbal communication. Inevitably, these physiological processes are also associated with psychological and psychosocial functions of tremendous significance to the individual. Because pain is acknowledged to be a subjective experience, the expression of dental and orofacial pain can be

influenced by such nonbiological factors as history, memory and learning associated with dental infection or facial trauma, past experience with dental treatment, attitudes towards the importance of maintaining the health of the oral structures through proper diet and oral hygiene practices etc. Hence, psychosocial factors play an important – some would say central – role in the perceptions, appraisals and behaviors of people when either dental or orofacial pain arises in such biologically and personally important parts of the body as the teeth, mouth and face.

Dental Pain

Pain located in the teeth and supporting intraoral bony structures is typically referred to as dental pain. The pathophysiological mechanisms giving rise to dental pain and the biologically based management of dental pain is presented in the chapter by Khan and Hargreaves (pp 75–90). Dental pain, with some important exceptions, is almost always *acute* (as opposed to chronic), arising relatively rapidly, usually readily localizable and typically associated with identifiable tooth pulp pathological or infectious inflammatory processes residing in the teeth and/or periapical tissues. An important exception, albeit not occurring frequently, is the *chronic* dental pain condition usually classified as atypical odontalgia (see the section Orofacial Pain below, and the chapter by Woda, pp 209–222). Here, a brief overview of the psychosocial components of acute dental pain is presented, and the most common biobehavioral methods for its management are indicated.

Patients seek out dentists for relief of dental pain that can reach excruciating levels when arising from toothache, periapical or periodontal infection and inflammation. The expectation that the dentist can relieve such pain has been a strongly positive association people hold about dentistry, and dentistry has, in fact, learned a great deal about pain and pain control, especially when the pain is acute and arising from local infection or trauma. Paradoxically, it is probably fair to say that most people living in economically developed and technologically advanced countries will actually experience very little pain arising from local dental or periodontal pathology in their lifetimes. For those people who come to the dentist pain free, concerns include apprehension that the dentist may cause pain, albeit understandably, in the course of providing optimal oral health care. But here, too, alleviation of the pain of dental procedures has been developed to a high degree, and dentists can realistically lead their patients to expect that pain from dental treatment is controllable – indeed, for most people requiring dental care, such pain associated with treatment is largely preventable. From the psychosocial perspective, the question for each dentist is

how best to respond to the accompanying anxiety or other emotions about going to the dentist and their attendant thoughts. Evidence shows that these psychological processes have a direct influence on acute pain threshold and tolerance levels, whether it is pain associated with treatments or postoperative pain, and whether it is the acute pain of dental, medical, surgical or invasive diagnostic procedures [4].

Psychological and Psychosocial Impact

As table 1 indicates, the psychological and psychosocial impact of dental pain is anxiety, more specifically fear and apprehension of current or anticipated dental pain. In a smaller number of cases, acute panic and phobic psychological states are caused by merely contemplating dental pain associated with dental treatment. Perhaps paradoxically, such heightened negative emotional states interfere not only with accessing and accepting necessary dental care, but often such anxiety-driven states are also associated with an inability or unwillingness to maintain positive oral health behaviors that could prevent dental disease associated with the very pain that these patients dread with often incapacitating anxiety.

The acute dental pain of dental infection – e.g. caries, periapical infection – is typically managed by a combination of anti-infectious agents and orally administered analgesics, typically nonsteroidal anti-inflammatory drugs, although sometimes narcotic medications may be indicated as well. While little attention has been paid to psychosocial methods for managing such acute dental infectious pain once it arises, much attention has been paid to uncovering whether or not psychological and behavioral factors contribute to the initiation of dental infection and eventually dental pain. Dentistry has a long and successful track record for advocating and educating with regard to improved preventive dental and oral health behavioral regimens specifically designed to maximize long-term oral health and minimize the risk for dental pain ever arising. The issues associated with patients not utilizing such preventive behaviors and proven methods for changing dental patient behavior with regard to preventing dental pain are well beyond the present scope. There are excellent resources available to dentists that comprehensively discuss the underlying psychosocial issues of accessibility, acceptability and prevention of dental disease and dental pain, often accompanied by practical recommendations for dentists to change maladaptive beliefs and behaviors that are risk factors for dental pain [5].

Behavioral Management

With regard to dental pain associated with dental treatment, it is undoubtedly the case in current dental practice that pain control for acute dental pain, whether associated with extreme anxiety, fear or phobia, is most often managed

in children and adults by pharmacological methods. These interventions range from topical and local anesthetics to intravenous and inhalation methods [6] for providing sedative-analgesic states safe and comfortable for most dental patients. Besides, more profoundly invasive general anesthesia is an alternative for the most resistant of anxious and phobic dental patients [7].

Fortunately, nonpharmacological methods that have a long and honorable history associated with ameliorating both dental anxiety and dental pain associated with treatment are available, which may be used in conjunction with dental pain pharmacotherapy or separately. Nonpharmacological management of dental pain and anxiety involves modifying the emotional and behavioral status of the patient by cognitive-behavioral methods. A wide variety of cognitive-behavioral methods are available to psychologically prepare the patient for clinical dentistry, with and without chemoanesthesia [4]. Cognitive-behavioral methods seek to change both the patient's thoughts, or cognitions, about dentistry – such as associating dentistry with thoughts of harm or pain – as well as the patient's dental behaviors – such as avoiding dental treatment. These methods range from provision of information to social modeling, and include biofeedback, formal hypnosis, individual and group counseling. Highly regarded clinical research by Berggren [8], Smith [9] and DeJongh et al. [10] has demonstrated the effectiveness of such methods and has clarified some of the underlying behavioral mechanisms for their efficacy. Clinically oriented texts [4, 5] provide useful perspectives together with specific methods to assist dental patients in the management of fear, anxiety and pain associated with dentistry.

Orofacial Pain

The most prevalent of orofacial pain conditions are musculoskeletal pain involving the masticatory muscles (often involving adjacent cervical muscles as well) and pain of the temporomandibular joints; collectively, orofacial pain conditions involving the masticatory muscles and temporomandibular joints are most commonly referred to as temporomandibular (muscle and joint) disorders (TMDs) [11]. Neuropathic orofacial pain conditions, whose prevalence is not so clearly established, but which are much less common, include trigeminal neuralgia and a collection of poorly understood and presumably neuropathic pain conditions commonly classified as 'persistent idiopathic facial pain' (formerly: 'atypical facial pain'). Intraoral soft tissue pain classified as 'burning mouth syndrome' [12] is also well known to dentistry [13]. (The chapter by Woda, pp 209–222, discusses issues related to the classification of orofacial pain; the preceding chapters of this section on orofacial pain entities present pathophysiological mechanisms and biological approaches to the management

of all these orofacial pain conditions.) For the sake of completeness, it should be noted that oral malignancies comprise a universe of diseases which often include pain as a prominent feature, but these are not included here.

The Challenge of Chronic Orofacial Pain

From public health and psychosocial perspectives, it seems most reasonable to consider all the orofacial pain conditions just mentioned as *chronic* orofacial pain problems – chronicity of these orofacial pain conditions is the risk factor that provides the greatest challenge to both societal costs and personal impact. Acute – that is, recently arising – orofacial pain is unquestionably encountered in clinical practice, but from a psychosocial perspective, the most important characteristics of orofacial pain arise in association with their clinically persistent and chronic nature. In fact, there is only a scant literature devoted to acute forms of the major orofacial pain conditions under consideration. Indeed, for the most part, the psychosocial perspectives and the behavioral management approaches for both acute and chronic orofacial pain of all types contain the same elements which all orofacial pain patients are at risk for. Table 1 summarizes the relationships among the most common elements influencing acute and chronic orofacial pain.

Chronic orofacial pain, which Bonica [14] referred to as a malefic force serving no useful clinical or personal purpose as a warning of trauma or disease, unfortunately remains for too many patients more resistant to quick or simple resolution. This is because the amount and even the location of pain experienced and the behaviors of the patient with persistent or chronic pain problems are only poorly related to physical events, making etiology elusive and treatment difficult. For example, atypical odontalgia and other neuropathic and soft tissue orofacial pains are often associated with poorly defined pathological markers disproportionate to the extent of expressed pain perception and pain behavior. Similarly, persistent pain in the masticatory muscles (myalgia) can be a source of minor inconvenience to some patients while for others it can become a decade-long major disorganizing force associated with significant depression and disruption of their everyday lives – yet there may be no detectable, let alone diagnosable, physical change to distinguish the two. So, whether persistent pain is experienced as a minor inconvenience or a source of major life stress, most often chronic orofacial pain and related psychosocial disability cannot be understood in terms of diagnosable pathology.

Behavioral neuroscience and modern neurophysiology have developed an emerging science of mind [15] which provides a biological basis for understanding how basic physiological processes subserving pain (see the chapters by Mense, Schaible, and Kopp and Sommer, pp 7–17, 18–27, and 28–43) as well as higher-order processes subserving emotional, thought and behavioral

processes, even including ethnicity and larger cultural influences, can become linked and stored as integrated neural circuits or neuromatrices [16], preserving memories and belief systems which influence subjective pain experience and guide actions taken to cope with pain. The complex interaction of these multiple dimensions of pain are also known to be under genetic influence (see the chapter by Stohler, pp 236–247) and reproductive hormonal cyclicity (see the chapter by LeResche, pp 44–55). The fact that patients often report pain in the absence of detectable tissue damage or pathophysiological cause can lead a well-meaning practitioner to attribute the pain to psychological rather than organic etiology. We find such a distinction of little practical value for chronic pain because there is usually no way to distinguish the two etiologies. If patients regard their experience as pain and if it is reported in the same ways as pain caused by tissue damage, it should be accepted as pain and treated accordingly. This perspective avoids tying pain to the stimulus, and it avoids the potential pitfall of deciding whether a patient's subjective report is reflective of real versus imagined pain. Instead, a more useful (and palatable for patients) view is that a pain report in the absence of discernible tissue damage can potentially arise from *multiple reasons (i.e. biological, psychological, social and/or cultural processes)* that invoke integrated multidimensional physiological activity which is experienced subjectively as pain.

Because musculoskeletal pain, particularly TMD-related pain, is overwhelmingly the most commonly occurring chronic orofacial pain confronting dentistry, with a prevalence of about 10–15% in the USA and around the world [17], and because TMDs are associated with the same significant psychological and psychosocial issues that are found in all chronic pain conditions, orofacial or otherwise [18, 19], much of the remainder of this chapter uses TMD-related pain to elucidate major concepts as well as methods for biobehavioral assessment and management. The psychosocial concepts and biobehavioral management methods pertaining to chronic orofacial pain conditions such as TMDs can be applied equally to chronic neuropathic and malignant orofacial pains, recognizing of course that some specific modifications in approach will be necessary to accommodate the different intra- and extraoral sites in which neuropathic, vascular and orofacial pains from malignancy might be located.

Biopsychosocial Model for Orofacial Pain: Rationale and Use

Mechanistic, biomedical views of pain as originating solely from somatic or physical pathology and requiring only objective assessment of pathophysiological processes, such as inflammation, are now considered scientifically inadequate to fully explain a chronic pain patient's presentation. It is now understood that health care providers have an inherent need to rely on patients as the only reliable source for knowing whether or not pain is present. We

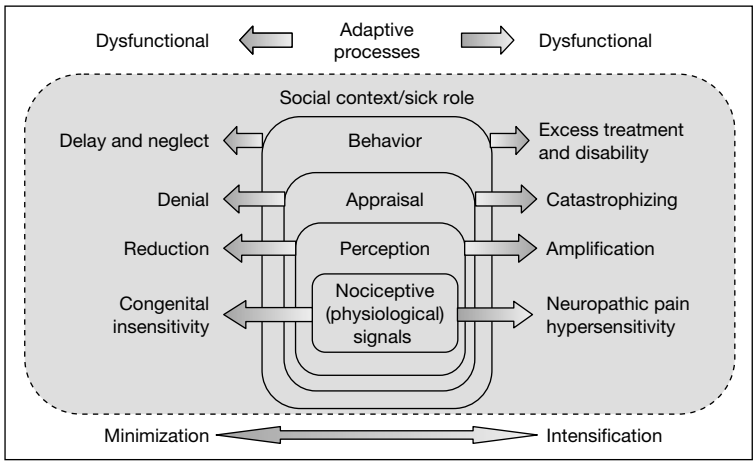

Fig. 1. Biopsychosocial model of chronic pain. The model's 5-stage processes integrate physiological or pathophysiological activity with associated psychological states and socially and culturally determined behavior.

simultaneously recognize that the subjective pain report is the result of many co-occurring factors, ranging from pathobiology to prior experience to social context. Hence, a purely biomedical model of pain has been outgrown because of its too exclusive emphasis on physical factors.

A model for integrating presumed physiological activity associated with ongoing pain experience, developed to guide research into the psychosocial aspects of orofacial pain, is depicted schematically in figure 1. Earlier versions of this biopsychosocial model have appeared elsewhere [20]. Its current version is reproduced because the concept of a biopsychosocial approach to disease and illness, in general, is not as widely known or accepted in dentistry as it is in medicine, where it has found virtually universal applicability. The model depicted as applied to pain derives from the seminal work of many biomedical, behavioral and public health scientists [1, 21, 22].

As the schematic figure 1 demonstrates, successively higher levels of central processing by the brain integrate the nociceptive or harmful stimuli present in the pain transmission system, eventually to emerge in consciousness as the individual's unique pain experience. Higher-order central processing assigns meaning to the pain for each individual, which then mobilizes patients to act within the social context of permissible behaviors, in response to their uniquely defined pain state. Because the model system seeks to integrate physiological or pathophysiological activity with associated psychological states and socially and culturally determined behavior, the model is labeled a *biopsychosocial*

model – that is, a model integrating biological, psychological and social components of the pain experience [20].

The stages of the pain experience offered by this model system all reflect normal or adaptive mechanisms by which individuals come to experience pain and then attempt to make sense of the pain and adapt appropriately. These same higher-order processes are subject to distortions and maladaptive responses as well, and some examples are given for each level, at which it is possible to analyze complex expressions of pain using this biopsychosocial model:

Nociception

Physiological events in the pain transmission system that, among other things, provides pain information to higher centers dealing with attention, memory, emotions, decision-making and motor preparedness.

Perception

The initial stage of forming a subjective pain response, self-identifying the *physical* qualities of the pain experience, which include *sensory* (e.g. sharp, dull, throbbing), *spatial* (e.g. highly localized to a specific anatomical site, as in acute toothache, or diffuse, as in many cases of temporomandibular pain) and *temporal* pain qualities (e.g. acutely arising, recent onset, as in toothache, or recurrent and persistent over time, as in chronic TMDs).

Appraisal

Higher-order integrative mental operations attaching cognitive and emotional meaning to the painful sensations being perceived. The appraisal level is crucial for attaching attitudes, beliefs, expectations and emotional arousal to those pain sensations – in a word, meaning is attributed to the physical experience. Inappropriate attribution of meaning, influenced by interaction of nociceptive activity with attention and memory, may yield cognitive thought processes and emotional states which show themselves as pain-related catastrophizing thoughts, fear, anxiety or depression.

Behavior

Observable pain behaviors that are either contributory (e.g. bruxism) or the result of pain (verbal and nonverbal expressions of pain, inactivity, diet modification). Fordyce's introduction of the notion of 'chronic pain behavior' into the rehabilitation of patients with chronic pain [21] was a revolutionary concept that called attention to the possibility for chronic pain conditions to become associated with maladaptive behavioral patterns of work or social avoidance. As a result, chronic pain treatment should not focus exclusively on uncovering difficult-to-observe pathophysiology, but should focus heavily on

behaviorally based methods for returning the pain patient to a more productive lifestyle.

Social Context: The Sick Role

Cultural and societal factors shape the pain experience by defining roles for pain patients that may sanction disability and provide specific forms of pain-related health care and medications. Sanctioning of different sick roles for women and men in response to pain is an important example of the influence that social factors can play in determining observable manifestations of pain. Options for treatment of dental and orofacial pain are often constrained by factors dictated by social or cultural factors, such as availability of health insurance and governmental regulation of narcotic analgesics. However, for a significant minority of patients experiencing chronic pain, the sick role is associated with heavy use of health care services and demand for narcotic pain medications, both examples of pain behaviors that can run counter to social norms in many parts of the world.

In summary, the biopsychosocial model, as its name implies, reflects our growing understanding that illnesses and cures are indeed complex; that to understand how and when we experience pain and to understand whether or not we will respond to treatment, a host of factors in addition to biology must be considered. The biopsychosocial model does not seek to compete with, let alone replace, scientifically derived biological models or current clinical practices. Rather, the model is an integrative one, which conceives that biological processes and environmental factors, in the broad sense defined earlier, are equipotent for explaining not only pain conditions, but also responses to treatment for the alleviation of pain.

A Dual-Axis Approach to Assessment of Dental and Orofacial Pain

From the above discussion, it is not surprising to find that currently no chronic pain problem is conceived of as either solely physical or mental, biological or psychological – either in the body, hence 'real,' or in the mind, hence 'imagined'. Instead of trying to force a particular patient with pain onto one end or the other of a single psychological-versus-somatic continuum, the biopsychosocial perspective suggests an alternative as figure 2 depicts: at least 2 axes be conceptualized for characterizing patients in pain; that is, that each patient be located on axis I, reflecting the status of physical/clinical factors that may yield a biologically based diagnosis, and axis II, reflecting psychological,

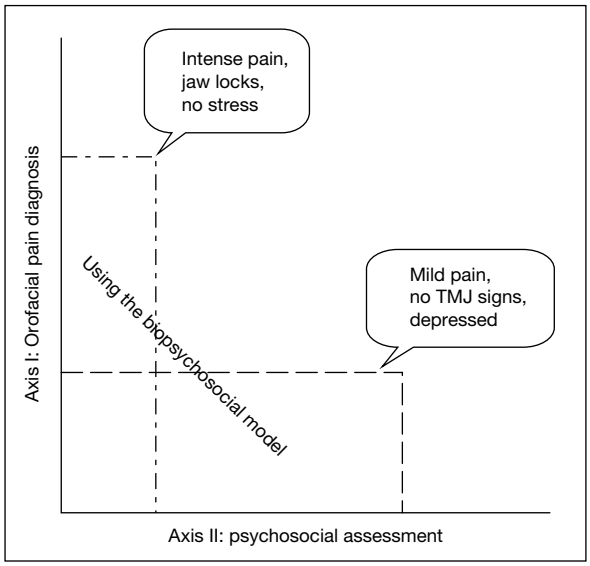

Fig. 2. Dual-axis approach for orofacial pain assessment. Axis I comprises the status of a patient's physical/clinical factors that may yield a biologically based diagnosis; axis II comprises an assessment of the patient's psychological, emotional and behavioral status. TMJ = Temporomandibular joint. Modified from Dworkin et al. [20].

emotional or behavioral and psychosocial status. The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) [22] use such a dual-axis approach for the diagnosis and assessment of TMD patients. The axis II components have been found to be reliable and valid as screening measures for depression, anxiety and psychosocial disability [23]; these measures are freely available at the website of the International Consortium for TMD Research (http://www.rdc-tmdinternational.org). It is important to note that the use of a dual (or even multiaxial) pain classification system such as that offered by the IASP [3] should not be misinterpreted to mean that the underlying concept is that orofacial pain is either in the body or in the mind. In fact the exact opposite is intended: orofacial pain is always, and in the most basic and fundamental terms, simultaneously in the body and in the mind; the mind is understood in this context to be one of many aspects of what the bodily processes generate. Clinically, the relevance of these notions is that orofacial pain is viewed by the clinician as a holistic and unified personal experience of the patient; for clinical expediency, orofacial pain can be analyzed from somatic and psychosocial perspectives, using the methods and languages relevant to each of those domains.

But the patient does not have such a dichotomous experience; the patient expresses a subjective experience, pain, which reflects the current resolution of the workings of the whole person.

Assessing Psychological and Psychosocial Factors

As a guide to assessing pain patients with regard to the contribution of psychological and psychosocial factors (axis II), 4 domains of such biobehavioral assessment are recommended: (1) pain history and response to prior treatment; (2) parafunctional oral behaviors (e.g. assessment of bruxism, pernicious oral habits); (3) psychological screening; and (4) interference with usual psychosocial functioning. From a practical treatment perspective, it should be noted that the assessment of these biobehavioral domains is possible largely by routine history and examination methods, supplemented with reliable and valid measures that are relatively easy for dentists to use and interpret [24].

Pain and Treatment History

Pain and treatment history are typically gathered as part of any new dental patient assessment. It is now strongly recommended that dentists gather data on the intensity of pain by the use of visual analogue or verbal descriptor scales, where patients simply mark a 100-mm line, anchored at one end with 'no pain at all' and the other end with 'the most intense pain imaginable' or respond to a verbal question using the same anchors. Such scales are used to assess average or typical pain intensity, worst pain and current pain intensity. With regard to treatment history, it is important to record the extent of prior treatment for chronic pain and the degree of success or failure of such past treatments. Repeated bouts of treatment failure often reflect a high risk for the failure of the next treatment.

Parafunctional Oral Behaviors

For the present purposes, this domain applies specifically to TMDs. There is very little known or even reported about parafunctional or other maladaptive behavioral habit patterns thought to be relevant to orofacial pains other than the musculoskeletal group of disorders classified under the term TMDs. The RDC/TMD include a measure for assessing potentially excessive jaw behaviors, such as jaw clenching and/or tooth grinding (bruxism). These behaviors are viewed as a significant risk factor by many for the initiation and maintenance of TMD-related orofacial chronic pain, although there has not yet emerged any clear scientific evidence to confirm the etiological role that jaw parafunctional behaviors may play. This measure and others in widespread use [25]

are straightforward and easy for dentists to apply, interpret and incorporate into their routine history protocols.

Psychological Status

Included here is the recommended screening assessment for depression, anxiety and the presence of multiple nonspecific physical symptoms, referred to in psychiatry as *somatization*. Formal assessment of psychological status requires specialized measurement instruments and/or diagnostic interview schedules beyond the training and expected clinical expertise of most dentists. However, the inclusion of relatively straightforward measures such as the Symptom Checklist 90 [26] in a clinical database, used routinely with all patients, minimizes resistance to the perception that attention is being unduly given to psychological factors when the patient feels that a physical pain problem is being presented. Such measures, although representing well-established psychological tests with excellent reliability and validity, are appropriate only as screening aids for psychological disturbance.

As included in the RDC/TMD axis II and as emphasized here, these psychological measures are not intended to be diagnostic of psychopathology (note: assessment of anxiety is not included in the original version of the RDC/TMD, but assessment of anxiety is recommended for all orofacial pain patients). This perspective on psychosocial assessment of orofacial pain patients allows dentists treating chronic orofacial pain patients to obtain a clearer understanding of the psychological status of the chronic pain patient in order to evaluate if there is either a need for more specialized psychological assessment or even whether the dentist is likely to be able to formulate a treatment plan which has a reasonable chance of succeeding because of the patient's emotional state.

Anxiety and panic are emotional disturbances seen not only in phobic dental patients but are increasingly recognized as concomitant psychological factors of chronic orofacial pain as well. These anxiety states are commonly seen during the acute phase of the orofacial pain problem when uncertainty over the meaning and future course of pain and any physical disease or other pathology that might underlie the pain is a dominant concern. Typically, as the pain becomes more chronic, depression becomes more prevalent, as initially co-occurring anxiety gives way to co-occurring hopelessness about the future and helplessness about finding a cure. Similarly, somatization [27], the subjective reporting of widespread, nonspecific physical symptoms is present to an excessive degree in a significant minority of TMD patients and is associated with such diverse consequences as presenting an important risk factor for poor TMD treatment outcome and for potentially confounding the accurate diagnosis of particular chronic orofacial pain conditions [28]. The presence of these somatization symptoms can be assessed with items found in the RDC/TMD axis II.

Psychosocial Status

Included here is the RDC/TMD axis II Graded Chronic Pain (GCP) scale, as a brief, evidence-based measure to assess the current level of psychosocial function [29]. The GCP scale has been used primarily in conjunction with RDC/TMD axis II assessment of chronic orofacial pain patients to assess, in a single index, both the severity of pain and the extent of pain-related interference with activities of daily living and extent of health care utilization (see <www.rdc-tmdinternational.org> for the 7 items comprising the GCP scale). Randomized control trials have shown the utility of using GCP as the criteria for assigning treatment, independent of axis I physical diagnosis [30, 31]. Prognosis is more guarded when self-reported activity limitations due to chronic pain are high and when pain interferes appreciably with the ability to discharge responsibilities at home, school or work and/or limits socializing activities (e.g. high GCP score).

Additional Useful Measures of Psychosocial Functioning

Multidimensional Pain Inventory

The Multidimensional Pain Inventory (MPI) [32] is an important and widely used instrument to assess psychosocial function in chronic pain patients. The MPI is much longer than the simple GCP scale, but more information for those who find it helpful in their clinical management and research to have a more detailed measure of psychosocial function. The MPI assesses pain impact (severity, interference), responses of others and activities, and enables patients to be classified into dysfunctional, interpersonally distressed and adaptive-coper subgroups. Such a categorization has also proven useful in treatment planning because studies have shown that dysfunctional patients improved more when treatment of depression was added to standard appliance and biofeedback therapy, and acute temporomandibular pain patients who were found to be dysfunctional and distressed on the MPI have been shown to be more likely to develop chronic temporomandibular pain while the dysfunctional profile has also been shown to predict treatment failure [33].

Substance Abuse

Substance abuse, principally with alcohol and narcotics, is frequently reported in the chronic pain and TMD literature to be more common than in the general population. Dentists may wish to consider the Alcohol Use Disorders Identification Test as a brief screen for these problems [34]. It uses 3 questions ('How often do you have a drink containing alcohol?' – 'How many drinks containing alcohol do you have on a typical day when you are drinking?' – 'How

often do you have 6 or more drinks on one occasion?'). An even briefer screen for both alcohol and drug abuse is the 2-Item Conjoint Screening Test ('In the last year, have you ever drunk or used drugs more than you meant to?' – 'Have you felt you wanted or needed to cut down on your drinking or drug use in the last year?'). These brief measures have been shown to have good sensitivity and specificity for detecting current substance use disorders [34].

Sleep Disturbance

Disturbed sleep is a potent dysregulator of homeostatic bodily processes, and sleep disturbance is consistently reported to be higher among chronic pain patients than in the population at large. The Pittsburgh Sleep Quality Inventory [35] is a widely used measure of sleep disturbance. Supplementing it with a single question – 'How is your sleep overall?' – may serve as an adequate screen to detect the possible presence of a sleep disturbance warranting further pursuit. Once acknowledged by the patient, there are therapeutic modalities available to enhance sleep hygiene, which range from medications to brief cognitive-behavioral therapy interventions.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can occur following the experience or witnessing of life-threatening events, such as military combat, natural disasters, serious accidents or violent personal assaults like rape. People who suffer from PTSD often relive the experience through nightmares and flashbacks, have difficulty sleeping and feel detached or estranged. These symptoms can be severe enough and last long enough to significantly impair the person's daily life. We have shown that in addition to being highly prevalent in chronic orofacial pain, patients with TMDs and PTSD present with a more complicated clinical picture that includes more intense pain and functional impairment when compared to those without PTSD [36].

There is good evidence supporting a synergy between chronic pain, including chronic temporomandibular pain and PTSD, but what remains unknown to date is the predictive value of routinely assessing PTSD in such TMD pain patients. However, it seems reasonable that screening measures be used in cases where PTSD is suspected. This can be done using the Clinician-Administered PTSD Scale 20 or the PTSD Checklist [37].

Physical and Sexual Abuse (Domestic Violence)

The literature contains numerous accounts of the frequent occurrence of physical and sexual abuse in patients with chronic temporomandibular pain. The lifetime prevalence of such domestic violence is estimated to be about 16%

of the American population. While women are the most common target of such abuse, men, the very young and the elderly are also targets.

Because the consequences can be so grave, and because the overwhelming tendency is to hide or deny any experience of abuse, it seems appropriate to recommend to clinicians treating patients where persistent pain is a dependable part of the clinical picture, that sensitive screening for issues of physical and sexual abuse be undertaken after a secure dentist-patient relationship has been obtained. The recommended assessment process is the so-called *AVDR* model: *ask* about abuse; provide *validating* messages; *document* presenting signs and symptoms; *refer* victims to domestic violence specialists [38].

In summary, a wide variety of psychosocial considerations may influence how orofacial pain patients express their pain condition. It has been suggested that dentists managing such patients screen for certain of these factors known to be prevalent, singly or in combination, in many orofacial pain patients. Once again, the data on this point are quite secure for TMDs, and there is much clinical evidence and conventional clinical wisdom that the same is true for the chronic neuropathic orofacial pain problems [39].

The Dentist as Biobehavioral Clinician: Guidelines for Managing Chronic Orofacial Pain

We have introduced the recommendation that dentistry extend its domain of clinical concerns to include the assessment and classification of psychological status and level of psychosocial functioning. Even more, we have suggested that dentists be encouraged to include in their clinical treatment armamentarium relatively simple cognitive-behavioral and behavioral techniques that can readily be applied by dentists to facilitate the amelioration of their patients' acute and chronic pain experiences [40].

The label 'biobehavioral' has gained acceptance as a collective term to refer to treatment approaches for chronic pain derived from applying behavioral science theories and methods to changing the perception and appraisal of pain and ameliorating or eliminating the personal suffering and psychosocial dysfunction that often accompany persistent pain conditions [41].

Dentists are uniquely well situated to deliver these biobehavioral treatment modalities, either themselves or in conjunction with appropriately trained members of the dental health care delivery team – dental hygienists are probably the best example – who are working directly under the supervision of both general practitioners and clinical dental specialists. Dentists often develop long-standing and effective relationships with many of their patients and are viewed as reliable and well-intended sources of information as well as technical expertise

when it comes to dental and orofacial problems of any sort. Our own and others' research has shown in repeated randomized clinical trials how cognitive-behavioral therapy, including use of education, relaxation and relapse prevention strategies, may be applied in general or specialty dental offices, by dentists or, in many cases of chronic TMD-related pain, by qualified members of the dental office staff [30, 31, 42]. The training to become both competent and comfortable with taking on the role of a biobehavioral clinician is easily within the level of expertise and ability of dental clinicians who are so motivated. Where direct delivery of biobehavioral orofacial pain management methods is not deemed possible in particular dental settings, clinicians may alternatively elect to refer those patients with chronic orofacial pain who have been identified by biobehavioral screening as burdened with heightened psychological or psychosocial disability to mental health professionals – psychiatrists, clinical psychologists and qualified psychiatric social workers.

The biobehavioral pain management modalities are drawn largely from cognitive-behavioral therapy as well as educational approaches. These psychologically based therapies include biofeedback, relaxation, imagery and hypnosis [43, 44]. Substantial evidence has emerged over the past two decades that such modalities are safe and effective in the management of chronic pain conditions. These biobehavioral treatments [45, 46] constitute a component of virtually every chronic pain treatment program, and the management of chronic orofacial pain, notably TMDs, has benefited from such biobehavioral interventions as well. Overwhelmingly, these methods emphasize as their common objectives self-management and the acquisition of self-control over not only pain symptoms, but cognitive attributions or meanings given to those symptoms and, most importantly, to maintaining a productive level of psychosocial function, even if pain is not totally absent.

By and large, when biobehavioral treatments are employed in the management of chronic orofacial pain, effects are virtually always positive and in the hypothesized beneficial direction, though often effects are moderate in size. These biobehavioral methods, especially those subsumed under the label 'cognitive-behavioral', appear to have the potential for producing long-lasting benefits that exceed those observed with the usual clinical treatment for TMDs. Increasingly, it should be noted that conservative, noninvasive approaches to TMD management are being advocated as the preferred overall treatment approach for this hard-to-understand chronic pain problem [47]. These so-called conservative treatments generally incorporate many of the same elements (i.e. relaxation, stress education, habit behavior modification etc.) found in cognitive-behavioral and biobehavioral therapies for TMDs. Thus, both the usual clinical treatment for TMDs and biobehavioral treatment employ multimodal approaches, and it does not yet appear possible to disengage which of the

multiple therapeutic components are most efficacious. If one method had to be singled out, relaxation seems to emerge consistently as an effective method for chronic pain management across a wide variety of pain conditions and over a wide variety of clinical settings. In any event, of the combined biobehavioral methods commonly used in clinical practice and in research, one method has as yet failed to emerge as superior to another.

It is important to note that much the same situation obtains with regard to biomedically based TMD treatments. Little is known about the superiority of any one of the multiple methods commonly employed to biomedically manage TMDs – there is no strong scientific evidence to substantiate invasive versus noninvasive treatments or pharmacological treatments emphasizing analgesics versus those stressing antidepressants or muscle relaxants. It is the absence of compelling evidence to the contrary which has led many clinical researchers to advocate conservative, reversible therapies for the largest number of TMD patients.

Conclusion

Psychological and psychosocial factors are universally accepted as prominent features among patients seeking treatment for amelioration of chronic orofacial pain, especially TMDs. Indeed, for a significant number of chronic orofacial pain patients, these pain-related emotional and behavioral factors may represent the major burden their condition imposes, putting an important stamp on the clinical presentation. While definitive information is not yet available regarding whether such emotional and behavioral factors are causes or effects of chronic orofacial pain states, it is nevertheless widely accepted that the comprehensive management of such patients requires attention to these issues. In practical terms, this means assessing levels of psychological and psychosocial disturbance in order to determine whether or not treatment decision-making should also include recommendations for incorporating psychological and/or behavioral management into comprehensive orofacial pain treatment. In terms of clinical utility for biomedical clinicians seeking to provide the most comprehensive treatment for their patients with chronic pain, 4 domains of psychological and psychosocial assessment are recommended: (1) pain; (2) parafunctional oral behaviors specific to each orofacial pain condition; (3) psychological status – principally depression – and somatization; and (4) psychosocial level of function as related to quality of life and use of health care services or medications. The RDC/TMD offer a battery of reliable and valid measures that have gained wide acceptance and use with TMDs. Psychological domains worthy of assessment but not incorporated into the RDC/TMD include anxiety, substance

abuse and sleep disturbance. Additional domains seemingly relevant to a comprehensive assessment of the orofacial pain patient – but again, the evidence is best for TMDs – include physical/sexual abuse and PTSD. Finally, the major thrust of this chapter has been to persuade the reader that a biopsychosocial approach – the model system that guides all major multidisciplinary pain centers – should be used by all clinicians treating orofacial pain patients. Current scientific evidence overwhelmingly confirms that this approach enhances both the understanding and the management of all chronic orofacial pain conditions.

References

1 Engel G: The need for a new medical model: a challenge for biomedicine. Science 1977;196: 129–136.
2 McHugh A, Vallis M: Illness behavior: operationalization of the biopsychosocial model; in McHugh S, Vallis M (eds): Illness Behavior: A Multidisciplinary Model. New York, Plenum Press, 1986, pp 1–31.
3 Merskey H, Bogduk N (eds): Classification of Chronic Pain, ed 2. Seattle, IASP Press, 1994, p 210.
4 Eli I: Oral Psychophysiology: Stress, Pain, and Behavior in Dental Care. Boca Raton, CRC Press, 1992.
5 Milgrom P, Weinstein P, Getz T: Treating Fearful Dental Patients: A Patient Management Handbook, ed 2. Seattle, University of Washington, 1995.
6 Yagiela JA: Recent developments in local anesthesia and oral sedation. Compend Contin Educ Dent 2004;25:697–706.
7 Manley MC, Skelly AM, Hamilton AG: Dental treatment for people with challenging behaviour: general anaesthesia or sedation? Br Dent J 2000;188:358–360.
8 Berggren U: Long-term management of the fearful adult patient using behavior modification and other modalities. J Dent Educ 2001;65:1357–1368.
9 Smith THL: Fear of dental care: are we making any progress. J Am Dent Assoc 2003;134:1101–1108.
10 DeJongh A, Adair P, Meijerink-Anderson M: Clinical management of dental anxiety: what works for whom? Int Dent J 2005;55:73–80.
11 Laskin D, Greene CS, Hylander WH (eds): TMDs: An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006.
12 Zakrzewska J, Forssell H, Glenny A: Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev 2005;25:CD002779.
13 Okeson J: Diagnostic classification of orofacial pain disorders; in Okeson JP (ed): Orofacial Pain: Guidelines for Assessment, Diagnosis and Management. Chicago, Quintessence, 1996, pp 45–52.
14 Bonica JJ: Chronic pain perspectives; in Bonica JJ (ed) The Management of Pain. Philadelphia, Lea & Febiger, 1990, vol 1.
15 Kandel ER: In Search of Memory – The Emergence of a New Science of Mind. New York, Norton, 2006.
16 Melzack R: Pain and the neuromatrix in the brain. J Dent Educ 2001;65:1378–1382.
17 LeResche L: Epidemiology of temporomandibular disorders: Implications for the investigation of etiologic factors. Crit Rev Oral Biol Med 1997;8:291–305.
18 Von Korff M, Dworkin SF, LeResche L, Kruger A: An epidemiologic comparison of pain complaints. Pain 1988;32:173–183.
19 Von Korff M, Dworkin SF, LeResche L, Kruger A: Epidemiology of temporomandibular disorders: TMD pain compared to other common pain sites; in Dubner R, Gebhart GF, Bond MR (eds): Pain Research and Clinical Management. Amsterdam, Elsevier, 1988, pp 506–511.

20 Dworkin SF, Von Korff M, LeResche L: Epidemiologic studies of chronic pain: a dynamic-ecologic perspective. Ann Behav Med 1992;14:3–11.
21 Fordyce WE: Behavioral Methods in Chronic Pain and Illness. St Louis, Mosby, 1976.
22 Dworkin SF, LeResche L: Research Diagnostic Criteria for Temporomandibular Disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord Facial Oral Pain 1992;6:301–355.
23 Dworkin SF, Sherman J, Ohrbach R, Truelove E, Mancl L, LeResche L: Reliability, validity and clinical utility of RDC/TMD axis II scales: depression, non-specific physical symptoms and graded chronic pain. J Orofac Pain 2002;16:207–220.
24 Dworkin SF: The case for incorporating biobehavioral treatments into TMD management. J Am Dent Assoc 1996;127:1607–1610.
25 Stegenga B, de Bont LGM, de Leeuw R, Boering G: Assessment of mandibular function impairment associated with temporomandibular joint osteoarthrosis and internal derangement. J Orofac Pain 1993;7:183–195.
26 Derogatis LR, Cleary PA: Confirmation of the dimensional structure of the SCL-90: a study in construct validation. J Clin Psychol 1977;33:981–989.
27 Katon W, Lin E, Von Korff M, Russo J, Lipscomb P, Bush T: Somatization: a spectrum of severity. Am J Psychiatry 1991;148:34–40.
28 Dworkin SF, Wilson L, Massoth DL: Somatizing as a risk factor for chronic pain; in Grzesiak RC, Ciccone DS (eds): Psychologic Vulnerability to Chronic Pain. New York, Springer, 1994, pp 28–54.
29 Von Korff M, Ormel J, Keefe FJ, Dworkin SF: Grading the severity of chronic pain. Pain 1992;50:133–149.
30 Dworkin SF, Huggins KH, Wilson L, Mancl L, Turner JA, Massoth D, LeResche L, Truelove E: A randomized clinical trial using Research Diagnostic Criteria for Temporomandibular Disorders-Axis II to target clinic cases for a tailored self-care TMD treatment program. J Orofac Pain 2001;16:48–63.
31 Dworkin SF, Turner JA, Mancl L, Wilson L, Massoth D, Huggins KH, LeResche L, Truelove EL: A randomized clinical trial of a tailored comprehensive care treatment program for temporomandibular disorders. J Orofac Pain 2002;16:259–276.
32 Kerns RD, Turk DC, Rudy TE: The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Pain 1985;23:345–356.
33 Rudy TE, Turk DC, Kubinski JA, Zaki HS: Differential treatment responses of TMD patients as a function of psychological characteristics. Pain 1995;61:103–112.
34 Bush K, Kivlahan D, McDonell M, Fihn S, Bradley K: The AUDIT alcohol consumption questions: an effective brief screening test for problem drinking. Arch Intern Med 1998;158:1789–1795.
35 Buysse D, Reynolds CI, Monk T, Berman S, Kuofer D: Pittsburgh Sleep Quality Index (PSQI); in Schutte N, Malouff J (eds): Sourcebook of Adult Assessment. New York, Plenum Press, 1995, pp 349–358.
36 Sherman JJ, McCubbin JA, Wilson DB, Carlson CR: Post-traumatic stress and chronic orofacial pain. J Orofac Pain 2005;19:309–317.
37 Blake D, Weathers F, Nagy L, Kaloupek D, Gusman F, Charney D: A clinician rating scale for assessing current and lifetime PTSD: the CAPS-1. Behav Res Ther 1990;13:187–188.
38 Curran S, Sherman JJ, Okeson JP, Carlson CR: Physical and sexual abuse among orofacial pain patients: linkages with pain and psychological distress. J Orofac Pain 1996;9:340–346.
39 Feinmann C, Newton-John T: Psychiatric and psychological management considerations associated with nerve damage and neuropathic trigeminal pain. J Orofac Pain 2004;18:360–365.
40 Dworkin S: The dentist as a biobehavioral clinician. J Dent Educ 2001;65:1417–1429.
41 NIH Technology Assessment Panel: Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia. JAMA 1996;276:313–318.
42 Dworkin SF, Turner JA, Wilson L, Massoth D, Whitney C, Huggins KH, Burgess J, Sommers E, Truelove E: Brief group cognitive-behavioral intervention for temporomandibular disorders. Pain 1994;59:175–187.
43 Sherman J, Turk D: Nonpharmacologic approaches to the management of myofascial pain disorders. Curr Pain Headache Rep 2001;5:421–431.

44 Vlaeyen J, Morley S: Cognitive-behavioral treatments for chronic pain: what works for whom? Clin J Pain 2005;21:1–8.
45 Turk DC, Meichenbaum D: A cognitive behavioral approach to pain management; in Wall PD, Melzack R (eds): Textbook of Pain. London, Churchill Livingstone, 1989, pp 1001–1009.
46 Turk DC: Customizing treatment for chronic pain patients: who, what, why. Clin J Pain 1990;6:255–270.
47 Greene C: Concepts of TMD etiology: effects on diagnosis and treatment; in Laskin D, Greene C, Hylander W (eds): TMDs: An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006, pp 219–228.

Samuel F. Dworkin, DDS, PhD, DSci (Hon)
4742 NE 178 Street
Lake Forest Park, WA 98155 (USA)
Tel. +1 206 363 6670, Fax +1 206 362 3439, E-Mail dworkin@u.washington.edu

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 209–222

A Rationale for the Classification of Orofacial Pain

Alain Woda

Dental Faculty, Université d'Auvergne, EA 3847, CHU de Clermont-Ferrand, Clermont-Ferrand, France

Abstract

Although medical taxonomy in general and the taxonomy of chronic pain in particular is a pragmatic affair, it needs to be based as far as possible on scientific evidence. This chapter reviews the strengths and weaknesses of the two main methods used to classify orofacial pain. Studies based on cluster analysis are particularly aimed at discerning different entities that might be seen at first glance as lying on a continuum of observed cases. Definition of diagnostic criteria, established from a selected group of subjects assumed to represent a single entity, is aimed at determining an objective, accurate, operational and reproducible tool to describe a single disease. An authority-based consensus originating from or organized by a scientific society or official institution is needed to consolidate the results, compensate for missing data and take into account the results of clinical and pure research on causes, mechanisms and clinical presentation. Several studies in the field of orofacial pain have used one or several of these approaches. They are reviewed and analyzed and constitute the basis of the new concept of classification proposed here, integrating neurological, idiopathic and neurovascular orofacial pain conditions.

Although medical taxonomy in general and the taxonomy of chronic pain in particular is a pragmatic affair [1], it needs to be based as far as possible on scientific evidence. The present chapter reviews the strengths and weaknesses of the usual methodologies used to classify orofacial pain. The results of recent studies based on cluster analysis are particularly examined.

Cluster Analysis Approach

The clinical reality of orofacial pain entities is characterized by a broad continuum of sign and symptom combinations with largely overlapping clinical

pictures, which are far removed from 'ideal' or 'typical' clinical presentations. The first problem encountered by scientists trying to classify such pain conditions is deciding what entities are to be specified. This question can arise at different levels; for instance: how many entities can be identified among temporomandibular joint (TMJ) and masticatory muscle disorders (i.e. temporomandibular disorders, TMDs), or how many for all head and neck pains? Multivariate analysis (cluster analysis) has sometimes been used to solve this type of problem. For example, the clustering pattern of patients with hip problems has been described [2]. This method has also been used to define subdivisions in ill-defined entities, such as complex regional pain syndrome [3], irritable bowel syndrome [4], chronic fatigue syndrome [5] and low back pain [6–9], as well as in several pain studies to determine prognosis and treatment orientations [10–17] largely based on psychopathological measurements [see references in 18]. Its use in orofacial pain has been limited to the impact of psychological and sociobehavioural factors [10, 11, 18–20].

Recently, this methodology was applied to the entire group of chronic orofacial pains in a prospective multicentric study carried out on 245 consecutive patients [21, 22]. The expectation was that the clustering of the signs and symptoms used as variables might reflect pathophysiological mechanisms and clinical significance. Each patient was seen by 2 experts; they administered a 111-item self-completed questionnaire, filled out a standardized 68-item examination form and proposed a diagnosis. These 179 items covered all the signs and symptoms needed to diagnose the various forms of orofacial pain conditions [1, 23–28]. After piloting and calibration, data were collected and processed in 4 steps:

- step 1: preselection of signs and symptoms by univariate analysis (χ^2 test) to select the significant signs or symptoms among the 179 questions;
- step 2: formation of composite signs and symptoms using a first cluster analysis.

Steps 1 and 2 yielded two lists of selected signs and symptoms. One of the two lists excluded signs and symptoms referring to a topographical site, organ or tissue so as to obtain a classification based on a list of non-topographical signs and symptoms.

- Step 3: clustering of the patients' conditions using multidimensional analyses;
- step 4: labelling of the clusters evidenced in step 3 by searching for the signs and symptoms characterizing the subjects of each cluster (decision tree); the labelling of each cluster was facilitated by unblinding the initial clinical diagnoses.

Steps 3 and 4 yielded a classification, the reliability of which was tested in randomized subsamples of the total sample. The validity of the results was

tested on the 107 patients suffering from the following 5 well-known orofacial pain conditions: migraines, tension-type headaches, cluster headaches, classical trigeminal neuralgia and posttraumatic trigeminal neuralgias. The reliability of the clinical diagnoses was also examined.

The strength of the cluster analysis approach is that it obviates any a priori decision. It can, therefore, be regarded as favouring an evidence-based classification of chronic orofacial pain. Cluster analysis also offers a way to classify the different entities hierarchically. It uses signs and symptoms, but it is possible to exclude those related to anatomical locations. Hence, it can be considered to be more closely related to the actual pain mechanisms [29] than classification systems based on tissues or organs. Some limits of this method must be noted, however. Although the groups identified by the cluster analyses are best characterized by the signs and symptoms displayed by the patients in each cluster, these signs and symptoms cannot be considered as diagnostic criteria, since their sensitivity and specificity have not been tested. However, diagnostic criteria could be determined for each cluster in a complementary investigation. Another limit of cluster analyses is that large groups of subjects are needed to individualize a disease. Therefore, only prevalent entities are readily identified. Ideally, several thousand patients need to be heard and examined, which can only be done in a complex multicentre multilingual study. Even then, this method might not identify diseases with very low prevalence. In addition, the representation of certain pain entities may be skewed by the patient recruitment, which is conducted in secondary or tertiary care settings. Thus, patients not commonly seen in primary care settings may be selected. Finally, there is some degree of tautology in the approach, since although cluster analysis can identify clusters of patients with similar signs and symptoms, it does not name the identified clusters. To label the clusters, some reference to a pre-existing classification is therefore unavoidable.

Approach Based on Authority-Based Consensus and Diagnostic Criteria

Most previous studies aimed at classifying pain diseases have been based on a different approach. Usually, the different groups of patients are defined on the basis of an a priori set of inclusion criteria used to select a group of patients representing a given pain entity. These inclusion criteria are generally based on an authority-based consensus [1, 26, 28]. Signs and symptoms or other variables observed in the selected patients are recorded and analysed according to their discriminating properties (sensitivity, specificity), giving a small set of diagnostic criteria used thereafter to characterize the chosen entity. The tautological

Table 1. Comparison of the two main methods used for building classification systems

Method for classification	What it can do	Limitations	Flaws	Advantages
Diagnostic criteria	Characterize an already selected group	A large fraction of the cases are left unclassified	Diagnostic criteria must be extracted from a group of patients chosen with pre-existing inclusion criteria *Circular reasoning*	Allows standardization of inclusions in clinical studies
Cluster analysis	Determine what entities really exist	Needs large sample Cannot define entities with very small prevalence	Observed groups must be labelled from a pre-existing classification *Circular reasoning*	Probably closer to mechanisms

nature of this approach prevents it being used to identify entities. In other words, the diagnostic criteria method does not say whether a group of cases belongs to a single disease or lies on a continuum of overlapping cases. This approach is, however, of great value in forming homogeneous groups of patients for research purposes. The scientific methodology used to determine these diagnostic criteria makes it possible to draw up consensual definitions that can be adopted worldwide by different groups of researchers. Another advantage is that relatively small numbers of subjects can be used to characterize a new disease. This is particularly helpful for rare diseases.

Critical Comments on the Two Approaches

The shortcomings of each approach can be summarized as follows: the cluster analysis method needs very large-scale studies and cannot identify low prevalence entities, while at the other extreme, the diagnostic criteria method can produce specious results, finding individualized diseases where there are none. Other considerations are summarized in table 1.

Even if the two methods are combined, there will still be room for a more subjective approach in which expert opinion will play the primary role. The

trend in the last few decades has been to rely on groups of experts rather than on individuals in order to control for 'individual leadership subjectivity'. However, scientific societies and institutions can also be subjective. Sometimes, this has resulted in conflicting classifications originating from different sources. An example can be found in the classifications of pain in the head and neck region into specific diseases, syndromes or pain entities that rely largely on work undertaken by the International Association for the Study of Pain (IASP) [1] or the International Headache Society (IHS) [28], later extended by the American Academy of Orofacial Pain (AAOP) [26]. Variations in these taxonomies can be largely explained by the academic background of the members of these groups (pain specialists, neurologists, dentists) who receive different patients or interpret similar or identical findings differently. As a consequence, each specialist proposes a classification oriented towards certain illnesses and away from others. The result is wide variations in taxonomies, in particular for orofacial pain entities. Even so, these classifications have proved over time to be invaluable in getting closer from a common worldwide language for clinical researchers.

Classification of Orofacial Chronic Pain: Results from Cluster Analyses

This section discusses the findings of a cluster analysis performed for chronic orofacial pain. In the leading taxonomic systems [1, 28], head and neck pain form a first division in chronic pain conditions. However, this division is already a limitation, because a single entity can display different signs and symptoms according to its location in the body and so may be classified differently by different specialists. For example, the individuality of the many 'functional syndromes' is widely debated [30, 31]. In addition, facial pain is frequently diffuse, extending largely outside the trigeminal field or even below the upper cervical dermatomes [32, 33].

If we accept this limitation, the next step should be to begin from as wide a point of view as possible. Three groups of orofacial pains can be recognized: (1) group of acute orofacial pains and (2) groups of chronic pains, i.e. what could be called 'neurological chronic pains' as opposed to 'idiopathic orofacial pains'. In the former are included well-known and well-described entities, such as classical trigeminal neuralgia, cluster headache and facial or cranial migraine, whereas the latter includes less well recognized, often disregarded yet no less prevalent pain entities, such as orofacial arthromyalgia, atypical facial pain and stomatodynia.

The cluster analysis data presented in figure 1 focus on the chronic orofacial pain conditions [21]. They are based on a list of variables devoid of anatomical

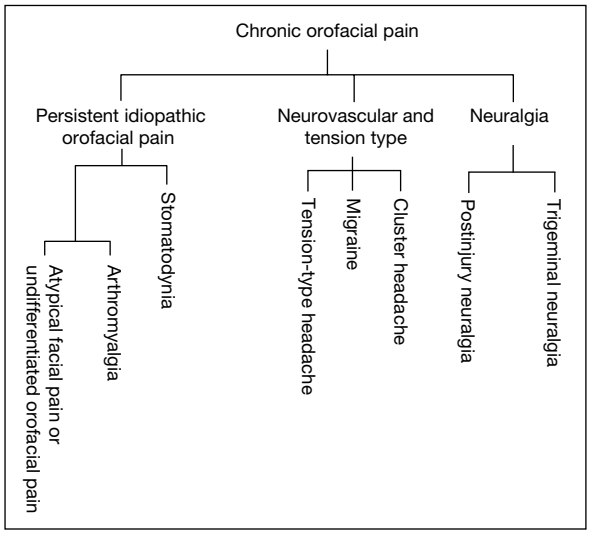

Fig. 1. Proposed classification for orofacial pain after multidimensional analyses. The term 'arthromyalgia' is intended to exclude the temporomandibular joint and masticatory muscle disorders with well-identified causes or mechanisms. 'Undifferentiated orofacial pain' includes the former atypical facial pain and atypical odontalgia. 'Persistent idiopathic orofacial pain' includes stomatodynia, arthromyalgia and undifferentiated orofacial pain. Since 'arthromyalgia' and 'undifferentiated orofacial pain' can be separated only by topographical signs and symptoms, they are located lower in the classification tree. Note that two clusters labelled as 'idiopathic orofacial pain' did not discriminate between the different idiopathic conditions. The cluster labelled 'stomatodynia', though clearly individualized, appeared to be linked to the other idiopathic conditions. Adding the topographical signs and symptoms separated 'arthromyalgia' from 'atypical facial pain' and 'atypical odontalgia'. 'Atypical facial pain' and 'atypical odontalgia' could not be individualized even with anatomical items. Therefore, these two clusters were labelled by a single term.

or organ landmarks. Figure 1 displays 3 groups of clusters with further branching forming a classification tree. Two observations can be made:

(1) The assembly of the two groups of neuralgic pain observed in figure 1 is the consequence of similarities between the signs and symptoms displayed by the patients forming these two clusters. The classical trigeminal neuralgia is found as an identified entity in all systems and manuals. The second cluster that we call 'postinjury trigeminal neuralgia' covers both the 'other terminal branch neuralgias' of the IHS [28] and the 'secondary trigeminal neuralgia' from facial trauma, which is common after orthognathic surgery and not rare after removal of impacted teeth [1]. Calling either of them 'neuropathic' would be misleading, because the definition and extent of

the neuropathic concept is ill defined [34] and other trigeminal pain entities located elsewhere in the tree are also probably 'neuropathic'.

(2) A second branch of the classification tree of figure 1 is devoted to persistent idiopathic orofacial pain. In the introduction of a classification for all types of pain, the experts of the IASP [1] place atypical facial pain under the heading 'some controversial issues'. The term 'atypical facial pain' is thereafter excluded from the IASP classification, while stomatodynia and atypical odontalgia are located between periapical periodontitis and cracked tooth syndrome on an anatomical basis. In the IASP classification, the two subgroups of muscle and TMJ pain (myofascial pain and TMJ arthralgia) are not separated. Conversely, in the last issue of the IHS, the term 'persistent idiopathic facial pain' is used to gather atypical facial pain and atypical odontalgia. 'Burning mouth syndrome' is classified nearby, but 'headache or facial pain attributed to temporomandibular joint disorders' is located far away in acute pain from the teeth or from the sinuses in that classification. The IASP, HIS and AAOP classifications show no current consensus [35] on the status of the different entities and the relationships among burning mouth syndrome (stomatodynia), atypical odontalgia, atypical facial pain and facial arthromyalgia (common form of TMDs). The results of the cluster analysis presented above clearly favour the view that idiopathic orofacial pain corresponds to a single disease expressed in different tissues: bone, tooth, oral mucosa, muscle and joint [27, 36–38]. It must be emphasized that the list of variables without topographical cues did not allow a clear separation between the different forms of idiopathic conditions, with stomatodynia being the only individualized subgroup. This indicates that the individualization of the other two entities (arthromyalgia and atypical facial pain) relies mainly on topographical criteria. It was only after the addition of items related to anatomy that entities, such as arthromyalgia and a common group associating atypical facial pain and atypical odontalgia, were identified.

Although terminology is not a crucial issue, the choice of certain terms must be explained. The present classification uses the term 'arthromyalgia' [36] rather than TMDs to exclude all conditions, the causes and mechanisms of which can be more easily identified, such as acute, often traumatic cases, including sprains or TMD problems linked to more general diseases [26]. A common group assembling atypical odontalgia and atypical facial pain has been placed under the heading 'atypical facial pain', because there is not enough new knowledge, e.g. in the pathophysiological field, to be more specific. The term 'atypical odontalgia' as a main heading cannot be accepted, since the painful area in atypical facial pain is often devoid of teeth [27]. The term 'undifferentiated orofacial pain' has been proposed given that the qualifying adjective 'atypical' may no

longer be accurate, because the clinical presentation is much better described and known now than it was 2 or 3 decades ago. In our opinion, a change in terminology should be considered after undisputed new knowledge has been gained, but this is not yet the case. The term 'persistent idiopathic facial pain,' which has recently been proposed [28] in place of 'atypical facial pain', could be used to qualify the entire idiopathic group, including stomatodynia and arthromyalgia. The term 'stomatodynia' is preferred to 'burning mouth syndrome', because a burning sensation within the oral mucosa may be caused by several kinds of other disease processes. Since in such cases it is only one symptom, it should not be confounded with what appears to be a true individualized disease (i.e. stomatodynia). It is common knowledge that stomatodynia is not a single symptom. Cluster analysis shows that it is not even a syndrome, but rather a very homogenous disease which, for the sake of its sufferers deserves more than merely a metaphoric appellation.

A third branch of the classification tree of figure 1 includes migraine and tension-type headache as observed after cluster analysis. Cluster headache was not individualized in the cluster analysis, probably because of the low prevalence in the sample. It has, however, been added in the primary branch of the tree.

A more general comment concerns the entire classification tree. By excluding all topographical landmarks, the resulting clusters are based only on the pain characteristics and not on location or causes. However, it is now agreed that an ideal classification of pains should be supported by mechanisms [29]. One of the main reasons for this is that mechanisms may change during the course of a single disease [see references in 39]. Nonetheless, patients report symptoms and not pain mechanisms, and until now diagnosing mechanisms in patients has been uncertain, to say the least. A pragmatic first step is, therefore, to refer to signs and symptoms to classify pain conditions. Signs and symptoms and mechanisms are most probably related, though not directly [40].

Classification of Orofacial Chronic Pain: Results from Authority-Based Consensus and Diagnostic Criteria Approach

Obviously, the above approach only concerns the first branches of the classification tree. The taxonomies proposed by the international institutions offer a large array of entities. For example, 19 separate entities are individualized and described in the 'migraine' section of the IHS [28]. In the first edition, the proposed entities were defined by diagnostic criteria mostly based on expert opinion. Later, these diagnostic criteria were re-assessed in numerous clinical studies, leading to new proposals. This trial-and-error approach produced a

renewed IHS classification [28]. Similar efforts have been made by the taxonomic committee of the IASP. The initial guidelines, published for TMDs by Charles McNeill [41], have been repeatedly updated by the AAOP [26]. Thus, these 'official' classifications must not be considered definitive. On the contrary, they must be tested and discussed in a continuous dynamic process. New proposals and rationales concerning the classification of neurological orofacial pain entities [35, 42–46], TMDs [20, 47–49] or other idiopathic orofacial chronic pains [27, 38, 50–52] are continuously being advanced.

Another development of the diagnostic criteria approach arises from the requirement that any ideal classification system should be exhaustive, i.e. that all patients should be diagnosed. In addition, the entities contained in any classification system should be mutually exclusive so that it should not be possible to assign two different diagnoses to one patient. However, these two requirements are generally not met, because diagnostic criteria have to be a compromise between two opposing properties, namely sensitivity and specificity. Consequently, a substantial proportion of patients cannot be diagnosed. For example, 29% of the patients seen in a tertiary care centre could not be diagnosed on the basis of the latest version of the IHS diagnostic criteria [53]. Also, many signs and symptoms are found in several entities, leading to double diagnoses. These limitations and conflicting requirements, together with the wide overlap of signs and symptoms in TMD subgroups, have led Dworkin, LeResche and coworkers to propose a new classification, the main characteristics of which are (1) the definition of a set of some 12 entities and (2) acceptance of multiple diagnoses [23, 24]. Each entity may be present independently or together with others in a single patient. Diagnostic criteria accurately define each subgroup of this classification, the primary aim of which is to standardize research efforts in the area, as emphasized by its usual designation: Research Diagnostic Criteria for Temporomandibular Disorders. This approach has improved the reliability of research findings by setting standards for clinical examination and clinical judgment. Knowledge of TMD-related pain has greatly increased as a result of the consequent improvement in standardization among research groups.

Classifications Based on Other Criteria or Other Needs

The results and reasoning outlined above are based on the assumption that signs and symptoms, including pain characteristics, are the consequence of somatic impairment. However, it is common knowledge that psychosocial and behavioural factors strongly influence chronic pain. Data corresponding to these pain-associated features have also been considered along with somatic

signs and symptoms for the classification of orofacial pain. Many different tools have been used to assess patients' psychological or personality status [18–20], the best known being the Multidimensional Personality Inventory [10, 11]. Using cluster analysis, they all confirmed the initial results of Turk and Rudy [10] that 3 groups of subjects could be identified: (1) a 'dysfunctional' group characterized by high scores for pain, life interference and emotional distress, and low scores for life control and activity; (2) an 'interpersonally distressed' group differentiated from the first group by a low level of social support, and (3) an 'adaptive copers' group displaying characteristics opposite to those of the dysfunctional group. A fourth group of patients was added later [18], called the 'repressor' group; it is described by high pain, low activity and low distress. It was suggested later that psychological factors were more important than the actual disease entity in terms of management and outcomes [11]. In addition, and although some psychological factors had been initially included in the diagnostic criteria of several forms of orofacial pain conditions, there is low correlation between somatic signs and symptoms and psychological factors. Accordingly, Dworkin and LeResche [23] have proposed considering separately an axis I, linked to somatic signs and symptoms, and an axis II, linked to psychological factors, each receiving a separate diagnosis and requiring separate treatment. This rationale is also supported by results of a cluster analysis which, by using signs and symptoms as variables, showed a totally distinct location of the somatic versus the psychological signs [21]. This is in full agreement with the statement of Turk and Rudy [11], which can be summarized as follows: a depression should be treated as such without considering whether the subject is also suffering from, for example, stomatodynia or a trigeminal neuralgia.

Lipton et al. [54] and Hapak et al. [55] were among the first to propose a classification of orofacial pain to be used specifically during an interview or with a self-questionnaire. In the absence of any clinical examination, the definition of the categories was inevitably approximate and the validity of the resulting data was not demonstrated until a recent study was conducted that could differentiate between musculo-ligamentous, dento-alveolar and neurological/vascular-based craniofacial pain [56]. Although of limited usefulness for diagnostic and management purposes, these classifications suit the large samples needed in epidemiological and treatment orientation studies.

Conclusion

Ideally, the construction of a classification should be based on two sets of data, each answering, at least partially, a conceptual need in the classification

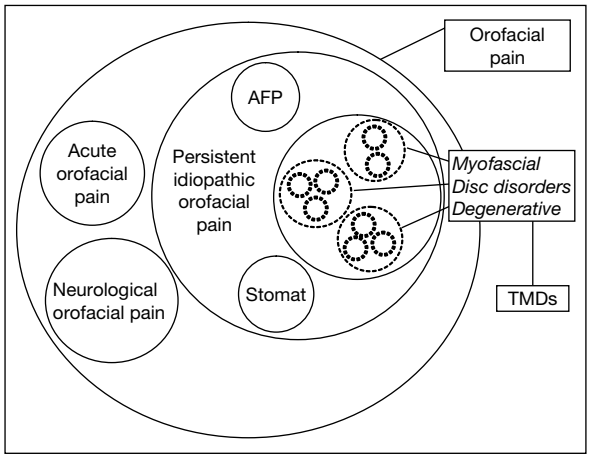

Fig. 2. Schematic representation of the main orofacial pain divisions. The entities which have not been clearly individualized from the others with a cluster analysis are represented with broken lines. The usual terminology for temporomandibular and masticatory disorders (TMDs) is given with their myofascial, disc disorders and degenerative clinical forms and the possible subdivisions that have been suggested. AFP = Atypical facial pain; stomat. = stomatodynia.

strategy. The first set of data should come from cluster analysis performed in a large group of patients presenting with a range of diseases. This is aimed at discerning different entities that might be seen at first glance as lying on a continuum of observed cases. The second data set should come from interactions between diagnostic criteria and authority-based consensus. The determination of diagnostic criteria performed in a selected group of subjects assumed to represent a single entity is aimed at defining an objective, accurate, operational and reproducible tool to describe a single disease. The authority-based consensus originating from or organized by a scientific society or an official institution is needed to consolidate the results, compensate for missing data and take into account the results of clinical and pure research on causes, mechanisms and clinical presentation. Ideally, the determination of diagnostic criteria for a group of subjects should follow the demonstration of an isolated entity. In the field of orofacial pain, interest has mostly focused on the analysis and identification of TMDs. However, the search for relationships between these pain conditions (TMDs) and other orofacial pain (fig. 2) may also supply crucial information.

References

1 Merskey H, Bogduk N: Classification of Chronic Pain: Description of Chronic Pain Syndromes and Definitions of Pain Terms, ed 2. Seattle, IASP Press, 1994.
2 Bierma-Zeinstra SMA, Bohnen AM, Bernsen RMD, Ridderikhoff J, Verhaar JAN, Prins A: Hip problems in older adults: classification by cluster analysis. J Clin Epidemiol 2001;54:1139–1145.
3 Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M: Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain 2002;95: 119–124.
4 Ragnarsson G, Bodemar G: Division of the irritable bowel syndrome into subgroups on the basis of daily recorded symptoms in two outpatients samples. Scand J Gastroenterol 1999;34:993–1000.
5 Jason LA, Torres-Harding SR, Carrico AW, Taylor RR: Symptom occurrence in persons with chronic fatigue syndrome. Biol Psychol 2002;59:15–27.
6 Coste J, Paolaggi JB, Spira A: Classification of non-specific low back pain. I. Psychological involvement in low-back pain: a clinical, descriptive approach. Spine 1992;17:1028–1037.
7 Coste J, Paolaggi JB, Spira A: Classification of non-specific low back pain. II. Clinical diversity of organic forms. Spine 1992;17:1038–1042.
8 Klapow JC, Slater MA, Patterson TL, Doctor JN, Atkinson JH, Garfin SR: An empirical evaluation of multidimensional clinical outcome in chronic low back pain patients. Pain 1993;55:107–118.
9 Langworthy JM, Breen AC: Rationalizing back pain: the development of a classification system through cluster analysis. J Manipulative Physiol Ther 1997;20:303–310.
10 Turk DC, Rudy TE: Towards an empirically derived taxonomy of chronic pain patients: integration of psychological assessment data. J Consult Clin Psychol 1988;56:233–238.
11 Turk DC, Rudy TE: The robustness of an empirically derived taxonomy of chronic pain patients. Pain 1990;43:27–35.
12 Strong J, Large RG, Ashton R, Stewart A: A New Zealand replication of the IPAM clustering model for low back patients. Clin J Pain 1995;11:296–306.
13 Crook J, Moldofsky H: The clinical course of musculoskeletal pain in empirically derived groupings of injured workers. Pain 1996;67:427–433.
14 Stiefel FC, de Jonge P, Huyse FJ, Slaets JP, Guex P, Lyons JS, Vannotti M, Fritsch C, Moeri R, Leyvraz PF, So A, Spagnoli J: INTERMED – an assessment and classification system for case complexity: results in patients with low back pain. Spine 1999;24:378–85.
15 Cook AJ, Chastain DC: The classification of patients with chronic pain: age and sex differences. Pain Res Manag 2001;6:142–151.
16 Weiner DK, Rudy TE, Gaur S: Are all older adults with persistent pain created equal? Preliminary evidence for a multiaxial taxonomy. Pain Res Manag 2001;6:133–141.
17 Fanciullo GJ, Hanscom B, Weinstein JN, Chawarski MC, Jamison RN, Baird JC: Cluster analysis classification of SF-36 profiles for patients with spinal pain. Spine 2003;28:2276–2282.
18 Burns JW, Kubilus A, Bruehl S, Harden RN: A fourth empirically derived cluster of chronic pain patients based on the multidimensional pain inventory: evidence for repression within the dysfunctional group. J Consult Clin Psychol 2001;69:663–673.
19 Butterworth JC, Deardorff WW: Psychometric profiles of craniomandibular pain patients: identifying specific subgroups. Cranio 1987;5:225–232.
20 Suvinen TI, Reade PC, Hanes KR, Könönen M, Kemppainen P: Temporomandibular disorder subtypes according to self-reported physical and psychosocial variables in female patients: a re-evaluation. J Oral Rehabil 2005;32:166–173.
21 Woda A, Tubert-Jeannin S, Bouhassira D, Attal N, Fleiter B, Goulet JP, Gremeau-Richard C, Navez ML, Picard P, Pionchon P, Albuisson E: Towards a new taxonomy of idiopathic orofacial pain. Pain 2005;116:396–406.
22 Zakrzewska JM, Woda A, Stohler CS, Vickers E: Classification, diagnosis and outcome measures in patients with orofacial pain; in Flor H, Kalso E, Dostrovsky JO (eds): Proceedings of the 11th World Congress on Pain. Seattle, IASP Press 2006, pp 745–754.
23 Dworkin SF, LeResche L: Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Pract 1992;6:301–355.

24 Truelove EL, Sommers EE, LeResche L, Dworkin SF, Von Korff M: Clinical diagnostic criteria for TMD, new classification permits multiple diagnoses. J Am Dent Assoc 1992;123:47–54.
25 Clark GT, Delcanho RE, Goulet JP: The utility and validity of current diagnostic procedures for defining temporomandibular disorder patients. Adv Dent Res 1993;7:97–112.
26 Okeson JP: Orofacial Pain: Guidelines for Assessment, Classification, and Management. Chicago, Quintessence, 1996.
27 Woda A, Pionchon P: A unified concept of idiopathic orofacial pain: clinical features. J Orofac Pain 1999;13:172–184.
28 Headache Classification Subcommittee of the International Headache Society: The International Classification of Headache Disorders, ed 2. Cephalalgia 2004;24(suppl 1):9–160.
29 Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjörk E: Towards a mechanism-based classification of pain. Pain 1998;77:227–229.
30 Wessely S, Nimnuan C, Sharpe M: Functional somatic syndromes: one or many? Lancet 1999;354:936–939.
31 Robbins JM, Kirmayer LJ, Hemami S: Latent variable models of functional somatic distress. J Nerv Ment Dis 1997;185:606–615.
32 Türp JC, Kowalski CJ, O'Leary N, Stohler CS: Pain maps from facial pain patients indicate a broad pain geography. J Dent Res 1998;77:1465–1472.
33 MacFarlane TV, Blinkhorn AS, Davies RM, Ryan P, Worthington HV, Macfarlane GJ: Orofacial pain: just another chronic pain? Results from a population-based survey. Pain 2002;99:453–458.
34 Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lanteri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29–36.
35 Zakrzewska JM: Classification issues related to neuropathic trigeminal pain. J Orofac Pain 2004;18:325–331.
36 Feinmann C: Idiopathic orofacial pain: a multidisciplinary problem: the contribution of psychiatry and medicine to diagnosis and management; in Campbell JN (ed): Pain – An Updated Review. Seattle, IASP Press, 1996, pp 397–402.
37 Harris M: The surgical management of idiopathic facial pain produces intractable iatrogenic pain. Br J Oral Maxillofac Surg 1996;34:1–3.
38 Woda A, Pionchon P: A unified concept of idiopathic orofacial pain: pathophysiologic features. J Orofac Pain 2000;14:196–212.
39 Rowbotham MC, Petersen KL: Zoster-associated pain and neural dysfunction. Pain 2001;93:1–5.
40 Jensen TS, Baron R: Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1–8.
41 McNeill C (ed): Temporomandibular Disorders: Guidelines for Classification, Assessment, and Management. Chicago, Quintessence, 1993.
42 Zakrzewska JM: Facial pain: neurological and non-neurological. J Neurol Neurosurg Psychiatry 2002;72(suppl 2):ii27–ii32.
43 Burchiel KJ: A new classification for facial pain. Neurosurgery 2003;53:1164–1167.
44 Bussone G, Tullo V: Reflections on the nosology of cranio-facial pain syndromes. Neurol Sci 2005;26(suppl 2):s61–s64.
45 Eller JL, Raslan AM, Burchiel KJ: Trigeminal neuralgia: definition and classification. Neurosurg Focus 2005;18:E3.
46 Siccoli MM, Bassetti CL, Sandor PS: Facial pain: clinical differential diagnosis. Lancet Neurol 2006;5:257–267.
47 Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT: Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). J Dent Res 2002;81:284–288.
48 Suvinen TI, Reade PC, Kemppainen P, Kononen M, Dworkin SF: 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 2005;9: 613–633.
49 National Institutes of Health: Management of temporomandibular disorders: National Institutes of Health Technology Assessment Conference. J Am Dent Assoc 1996;127:1595–606.

50 Pfaffenrath V, Rath M, Pöllmann W, Keeser W: Atypical facial pain: application of the IHS criteria in a clinical sample. Cephalalgia 1993;12:84–88.
51 Mongini F, Ciccone G, Ibertis F, Negro C: Personality characteristics and accompanying symptoms in temporomandibular joint dysfunction, headache, and facial pain. J Orofac Pain 2000;14:52–58.
52 Melis M, Lobo SL, Ceneviz C, Zawawi K, Al-Badawi E, Maloney G, Mehta N: Atypical odontalgia: a review of the literature. Headache 2003;43:1060–1074.
53 Zebenholzer K, Wober C, Vigl M, Wessely P, Wober-Bingol C: Facial pain in a neurological tertiary care centre – Evaluation of the International Classification of Headache Disorders. Cephalalgia 2005;25:689–699.
54 Lipton JA, Ship JA, Larach-Robinson D: Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 1993;124:115–121.
55 Hapak L, Gordon A, Locker D, Shandling M, Mock D, Tenenbaum HC: Differentiation between musculoligamentous, dentoalveolar, and neurologically based craniofacial pain with a diagnostic questionnaire. J Orofac Pain 1994;8:357–368.
56 Macfarlane TV, Blinkhorn AS, Craven R, Zakrzewska JM, Atkin P, Escudier MP, Rooney CA, Aggarwal V, Macfarlane GJ: Can one predict the likely specific orofacial pain syndrome from a self-completed questionnaire? Pain 2004;111:270–277.

Alain Woda
Professor
Dental Faculty, Université d'Auvergne, EA 3847
11, Boulevard Charles-de-Gaulle
FR–63000 Clermont-Ferrand (France)
Tel. +33 4 73 17 73 27, Fax +33 4 73 17 73 09, E-Mail alain.woda@u-clermont1.fr

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 223–235

Orofacial Pain: Past and Future

Charles S. Greene

Department of Oral Diagnosis and Diagnostic Sciences, College of Dentistry, University of Illinois at Chicago, Chicago, Ill., USA

Abstract

This chapter provides a historical perspective on the subject of orofacial pain and temporomandibular disorders (TMDs). Unlike some other medical or dental concepts that have developed in an orderly fashion, the thinking about these disorders has been uneven and contentious over the past 75 years. Much of this controversy can be attributed to the subjective nature of the major symptoms of these conditions, which makes them difficult to diagnose in a definitive manner. However, there are other factors within the dental community that have contributed to these disputes, and as a result the field continues to be controversial. The most significant arguments have been about the etiology of various TMDs, which naturally has strongly influenced the choice of suitable therapies for TMD patients. Because many TMD patients tend to respond positively to quite dissimilar treatments, their successful clinical outcomes have only served to make things more confusing. However, current research is focused more heavily on the underlying mechanisms of muscle and joint pain as well as the neurophysiological mechanisms of acute and chronic pain. In addition, the behavioral effects of being a chronic pain patient are finally getting the attention they deserve. Therefore, the future looks promising for a better understanding of both the scientific and the clinical aspects of these complex problems.

In some areas of human intellectual activity, there is an expression that describes the flow of ideas and events: ‘The past is prologue to the future.’ However, when the past ideas or events have not been notable for their good features, people might want to move ahead in entirely new directions. This chapter, which appears in an excellent book on modern orofacial pain (OFP) concepts and practices, is intended to show where we have been and where we are going in that field, with special focus on the temporomandibular disorders (TMDs). My premise is that during the past 75 years, we have been down some dark roads intellectually, and this has had an unfortunate effect on both

practitioners and patients [1]. Yet, thanks to the extraordinary efforts of some prominent researchers and clinicians, much progress has been made in achieving better diagnostic and therapeutic outcomes. Today, the field of OFP stands poised on the threshold of deeper scientific understanding and better clinical management of OFP phenomenology [2]. While some people continue to argue about historical concepts and to resist changing their clinical practices, it has become clear that these disputes belong to the past, and that the future holds great promise for caring practitioners as well as for suffering patients.

Early Concepts and Their Consequences

The conditions which today are called TMDs initially emerged from outside the dental profession as well as within it. While some early dental clinicians had written papers describing various jaw pain and dysfunction symptoms [3–8], it was an otolaryngologist (J.B. Costen) who wrote the seminal articles about this condition in the 1930s. As part of his formulation of the eponymous Costen's syndrome [9], he attributed the condition to overclosure of the mandible which produced pressure on various anatomic structures in the area of the temporomandibular joint (TMJ) and the nearby ear region. It is important to mention that Costen was writing as a clinician speculating on causal mechanisms, not as an anatomist, and eventually most of his concepts were found to have no anatomic basis [10, 11]. Yet, his articles seemed to galvanize the dental profession into taking responsibility for treating these problems, which were referred to as TMJ syndrome (but never as OFP problems).

The concept of an overclosed mandible (a common situation in those times, due to extensive loss of teeth in the general population) led logically to procedures for 'opening the bite'. This, of course, was something that dentists could accomplish in many ways, the easiest of which was simply to make dentures for edentulous people. However, when people with all or most of their teeth intact presented with the symptoms of Costen's (TMJ) syndrome, they were also subjected to bite-raising procedures using oral splints and fixed or removable dental prostheses [12]. This was an important milestone in the evolution of the TMD field, because the clinical outcomes of such treatments would either encourage or discourage clinicians to continue in this direction. Unfortunately, many of the patients appeared to get better while being treated in this manner, setting the stage for many similar phenomena over the succeeding years. It was not until the 1960s and 1970s that anybody challenged the validity of both the underlying theories and the clinical outcomes of these early treatment concepts.

The Age of Craniomandibular Perfection

As far back as the 1940s and 1950s, some dental clinicians were writing and talking about various 'ideal' craniomandibular relationships. These included condyle-fossa alignment, symmetries of facial and jaw bones, and intra- as well as interarch occlusal relationships. These concepts emerged more strongly in the succeeding decades, as gnathologists defined ideal TMJ centric relations, prosthodontists defined ideal vertical dimensions, orthodontists defined ideal intermaxillary relationships, and various other clinicians postulated ideal muscle harmony and balance concepts [13–18]. In virtually every concept, the definition of 'ideal' was quite narrow and precise, leaving much of the population outside of the ideal category. The TMD patients who were seeking help during those years were usually analyzed in terms of their anatomic and physiological imperfections, leading to various corrective dental procedures to bring them into more ideal relationships. Interestingly, nonsymptomatic people who were examined in dental offices were often described as being 'resistant' to their anatomic imperfections, but still some were treated 'prophylactically' to prevent future troubles.

Again, it was many years before anatomists, physiologists and other craniofacial researchers were able to demonstrate that much of what was being called imperfection was, in fact, nothing more than normal biological variation within populations. Clinical population studies eventually showed that none of these morphological or functional variables were either convincingly or consistently associated with any specific TMD problems [19–21].

The Introduction of Psychosocial Factors

The possibility that psychosocial factors might be important in developing or maintaining symptomatic TMDs first emerged in the 1960s. The entire field of psychophysiology had been given a running start many years earlier by the work of Hans Selye [22], who demonstrated the physiological responses of various body systems to environmental stressors. However, it took a long time for either the medical or dental professions to begin applying these concepts to the illnesses of their patients. The work of Lazslo Schwartz and Joseph Marbach at Columbia University [23], followed by the work of Daniel Laskin and Charles Greene at the University of Illinois [24], introduced this perspective into the field of TMDs. It was not long, however, before questions arose about which psychosocial variables were really important. Were TMD patients anxious, depressed, neurotic or hypochondriacal? Did they have diagnosable personality disorders? Did they suffer from classifiable psychiatric illnesses? Or were they

mostly normal people who were reacting to excessive stress in their lives, or who had poor coping skills for dealing with stress?

The answers to all of these questions are quite complex and have been addressed in several other publications [25–29] as well as elsewhere in this book (see the chapter by Dworkin, pp 187–208). Eventually, it did become clear that most TMDs were biopsychosocial disorders that affected (mostly) psychologically normal people, but the persistent pain of these disorders could produce significant psychosocial effects. As discussed by Dworkin in his chapter (pp 187–208), this concept became the basis for developing the Research Diagnostic Criteria for TMDs, which incorporate a physical examination (axis I) with a psychosocial assessment (axis II) [30]. Other TMD authorities have proposed hybrid hypotheses of etiology, in which the term 'multifactorial' has been used to make those concepts sound more intellectual, but no specific combinations of anatomic and psychological factors have been consistently demonstrated in TMD patients [31] (table 1).

The Dilemma of Clinical Success (and Failure)

Until the 1960s, no systematic clinical studies had been conducted to evaluate the efficacy of treatments for patients with TMDs. Instead, there were a number of 'scorecard studies' published that reported high levels of successful treatment for these patients, utilizing a variety of mechanical (dental) approaches. As often happens, for many clinicians these clinical successes seemed to support the assumptions underlying their use. Even worse, the failure of a minority of patients to respond positively to such treatments was seen as a sign of psychological disturbance (e.g. hypochondriasis, depression, malingering, secondary gains) rather than a sign of inappropriate or ineffective treatment. Unfortunately, failure to respond to a therapy was often used as the basis for attempting a more aggressive therapy, up to and including surgical procedures. When some early TMD studies in the 1960s and 1970s reported rather high levels of positive response to placebo treatments [21, 32, 33], these findings were dismissed as being some type of trickery. Some investigators were even accused of misleading or duping patients by using placebos instead of 'real' treatments.

During that same time period, a number of controlled TMD treatment studies were producing high rates of positive response without performing any irreversible dental or skeletal corrective procedures [34–39]. In addition, longitudinal follow-up studies showed that these short-term favorable responses often persisted over periods of many years, even if the original treatment was only a placebo [40–49]. This accumulating evidence presented a powerful argument against the use of traditional mechanical TMD therapies, especially

Table 1. Relationships among diagnosis, etiology and treatment in TMDs

Standard	Diagnosis	Etiology	Treatment	Prevalence
Ideal	Clear and correct Measurable Demonstrable	Specific Measurable Treatable	Antietiological Definitive Successful	Not achievable at this time
Acceptable	Presumptive Probably correct Categorical labels	Unclear Complex Reversible	Empirically validated Matched to diagnosis Conservative	Frequently achievable; represents best current practice
Wrong/bad	Parochial specialty labeling Technological diagnosis Possibly correct	Favorite theory Morphofunctional analysis Mechanical concept	Prolonged appliance wear Bite-changing procedures Jaw repositioning	Most common current practice, despite lack of scientific foundation
Outrageous	Misdiagnosis of pain Neglect of serious pathological conditions Neglect chronicity	Guru/cult concepts Quackery concepts Parochial specialty concepts	Whole-body procedures Quackery procedures Extreme dental procedures	All too common; represents fringe of current practice

Adapted from Greene [31].

since the irreversible nature of those treatments could significantly complicate a nonresponding patient's condition, both physically and psychologically [50–52]. Finally, even for those TMD patients who were treated successfully, some serious questions remained:

(1) How much of their positive response was due to a placebo effect or even to a general phenomenon of 'doctor's white coat' cure?
(2) How much improvement in symptoms was due to the natural fluctuation of their condition or to a 'regression to the mean' level of symptoms?
(3) How much treatment was really necessary to achieve a good outcome for each individual patient's problem?

The answers to questions like these are crucial to making a distinction between sufficient versus excessive treatment for any condition. Space does not permit a full discussion here about this topic, but for most cases of TMD it has

become clear that the line between reversible and irreversible treatments does not often need to be crossed in order to produce good clinical outcomes [52].

Widening the Scope of 'Temporomandibular Disorder' Diagnosis

While dentists were struggling with the issues of correctly diagnosing and properly treating TMD patients, advances in the study of pain neurophysiology and craniocervical pain disorders began to have their impact on our profession. As far back as the 1970s, Welden Bell had begun to speak of OFP as the umbrella term for the conditions we were dealing with – whether we realized it or not [53]. Many facial pain patients during the transition years of the 1980s and 1990s (and even currently) have been misdiagnosed as having a TMD when, in fact, they had a neuropathic or neurovascular pain problem. Unfortunately, the training of most dentists (and most physicians as well) had not prepared them for this broader challenge, and as a result many of their patients did not receive a proper diagnosis for a long time. Recent studies [Scrivani, unpubl. data] have shown that both physicians and dentists could be as much as 18–24 months late in establishing a diagnosis of trigeminal neuralgia, which is one of the more classic types of neuropathic pain that should be easily recognized.

Within the dental profession, this situation has been improving gradually due to the creation of several postgraduate university programs in OFP, as well as many articles, lectures, continuing education courses and books like this that deal with this topic. In addition, some dental schools are beginning to teach this subject at the predoctoral level with more emphasis, but that is not yet a universal fact [54].

Emerging Concepts of Temporomandibular Disorder Pathophysiology

Given what we now know about the biochemical and neurophysiological basis for musculoskeletal pain disorders [55–58], some of our old notions about why joints or muscles hurt seem almost laughable. Likewise, the explanations for why pains persist in some people and not others have switched almost completely from the field of psychology to the field of neuroscience [59]. These topics of pathophysiology are covered well in other chapters of this book, but they are mentioned here briefly as an important transitional bridge to the future of this field. There is little doubt that future therapies in the pain field will be targeted more precisely toward underlying pathophysiological mechanisms of joint pain, muscle pain and chronic pain, rather than at simple analgesia or other pain control mechanisms.

The most important 'new' concept in the field of pain is definitely the discovery of neuroplasticity of the nervous system. Ever since René Descartes (1596–1650), the model for understanding pain transmission was the same model that explained how a telephone switching exchange works. The nervous system was viewed as a passive set of transmission lines, waiting to be activated and then forwarding the message onward and upward to elements of the central nervous system (CNS). When Melzack and Wall [60] first presented their 'gate control theory' of pain in 1965, which postulated an active role for components of the CNS to affect the transmission of pain signals both positively and negatively, few could anticipate how powerful the impact would be from that theory and subsequent discoveries. Today we understand that pain can arise spontaneously, or it can be elicited by stimuli as small as touch or as large as crushing trauma, and from that initial event many outcomes are possible – including lingering pain, spreading of pain and even lifelong persistence in the worst-case scenarios. For further discussion of these phenomena, the reader is urged to see the chapters by Schindler and Svensson, pp 91–123, Sessle, pp 56–74, and Zakrzewska and Renton, pp 165–186.

Outcome Research – Effect on Clinical Management

As mentioned earlier in the section on clinical success and failure, the outcomes of treating patients play a powerful role in shaping the thinking of clinicians. It is this 'clinical bias' which must be controlled for in setting up treatment studies, where the patients will be evaluated within a 'controlled' protocol utilizing double-blind therapies and assessments whenever possible. The last 30 years have seen a major proliferation of these kinds of randomized clinical trials in the field of TMDs, as well as in the broader field of OFP and pain in general [61–64]. In the TMD field, most of these controlled studies have demonstrated high levels of positive responses to conservative treatment strategies, which are generally successful as often as most irreversible ones [21, 65]. Nevertheless, the arguments persist about the 'need' for more aggressive biomechanical therapies in order to produce a more 'definitive cure', a concept which is especially inappropriate for patients with chronic OFP conditions.

Likewise, the broad research support for conceptualizing TMDs within a biopsychosocial framework has failed to persuade a number of clinicians who still adhere to biomechanical concepts of etiology and treatment. Further evidence for viewing TMD and OFP patients in a broader framework has come from studies showing high levels of comorbidity of these conditions with other functional disorders [66–68]. For many of these patients (especially the chronic ones), a systemic dysregulatory disorder involving the CNS and the

hypothalamic-pituitary-adrenal axis (HPA) has been proposed and demonstrated [69, 70], but still many of our colleagues continue to ignore the importance of these findings. Finally, the failure to understand chronic pain phenomenology has led many clinicians into the swamp of escalating mechanical pain therapies when conservative treatments do not appear to be working. This is especially unfortunate when the more aggressive treatments involve surgeries or other irreversible morphology-changing procedures [71–73].

Future Directions

The future of the TMD/OFP field will be determined by the progress that is made in the larger field of pain management. Multitudes of researchers around the world are looking at both basic science and clinical paradigms that will change the way we look at pain in general. At this time, there are three main areas of focus for these investigations:

1 *Genetics* – As discussed in the chapter by Stohler (pp 236–247), evidence is accumulating about the role of genetics in susceptibility to pain as well as in the variable responses to having pain. Some studies have already demonstrated a genetic difference between people's reaction to experimental pain [74], while others have shown that it may be possible to predict who will have painful conditions arise later [75]. The implications of these findings for the management of pain patients are only beginning to be understood. Even in the absence of genetic manipulation, which may be a futuristic strategy, clinicians can utilize current modalities and strategies more wisely if they know who they are dealing with.

2 *Pathophysiology* – It seems that every new edition of the major pain journals brings more information about the molecular chemistry and biology of various types of pain [76–79]. In the case of the TMJ, the discovery of inflammatory mediators and neurochemicals within the joint has led to a much better understanding of what is happening in painful conditions, and already some therapies are being tested for controlling these factors [80–83] (see the chapters by Schaible, Kopp and Sommer as well as Steenks et al., pp 18–27, 28–43, and 124–152). The same is true for muscular pain, although the pathophysiology of that type of pain is less well understood at this time [57, 58, 84–86] (see the chapters by Mense as well as Schindler and Svensson, pp 7–17, and 91–123). As more information emerges, treatments directed at the underlying pathophysiology of painful conditions will inevitably be more successful than treatments that only suppress pain or inflammation.

3 *Predictive factors* – Some success has already been reported in identifying physical and psychological factors in OFP patients that may predict their

responses to therapy [87, 88] (see the chapters by LeResche and Dworkin, pp 44–45, and 187–208). The search for more predictors should enhance the ability of clinicians to develop appropriate treatment plans that are individualized for each patient.

Finally, it is important to realize that chronic pain is a condition that, to paraphrase Benjamin Crue's definition [89], no longer has much to do with whatever caused it to begin in the first place. The implications of this fact are profound for chronic pain sufferers, because it means that clinicians should try to avoid specific and aggressive treatments that will 'cure' their problems. Instead, strategies directed at their centrally maintained pain conditions as well as their psychosocial well-being need to be tailored to their individual problems [90]. This approach is already being applied in many academic centers and special pain management programs, but it also needs to be understood by frontline practitioners in both medicine and dentistry so that they can provide appropriate care in their offices.

Conclusion

Hopefully, this brief historical review of the TMD/OFP field will help readers to understand how the past and present thinking in this field has influenced, and will continue to influence, our journey into the future. As stated at the outset, the dental profession is not bound by its past mistakes or ignorance as we attempt to move forward, but the failure to recognize those flaws will certainly impede our progress. Fortunately, when it comes to the subject of pain, the medical, dental and scientific communities have been converging toward each other in the past 20–25 years. As a result, there is no longer any value in having separate 'dental' terminology or parochial theories to define and explain OFPs, since they are merely a subset of the larger universe of human pain conditions. Furthermore, as evidence-based practice becomes the ethical standard for all clinical endeavors, we will need to join our fellow health practitioners in trying to provide the best care possible for our patients. Doing so will require knowledge about what is happening to our patients both physically and psychologically so that the selection of treatments for them can follow the 'Three Bears Rule': not too much, not too little, but just the right amount.

References

1 Greene CS: Temporomandibular disorders: the evolution of concepts; in Sarnat BG, Laskin DM (eds): The Temporomandibular Joint: A Biological Basis for Clinical Practice, ed 4. Philadelphia, Saunders, 1992, pp 298–315.

2 Greene CS: Concepts of TMD etiology: effects on diagnosis and treatment; in Laskin DM, Greene CS, Hylander WL (eds): TMDs: An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006, pp 219–228.
3 Prentiss HJ: A preliminary report upon the temporo-mandibular articulation in the human type. Dent Cosmos 1918;60:505–514.
4 Summa R: The importance of the inter-articular fibro-cartilage of the temporomandibular articulation. Dent Cosmos 1918;60:512–514.
5 Wright WH: Deafness as influenced by malposition of the jaws. J Nat Dent Assoc 1920;7: 979–990.
6 Monson GS: Impaired function as a result of closed bite. J Nat Dent Assoc 1921;8:833–839.
7 Decker JC: Traumatic deafness as a result of retrusion of condyles of mandible. Ann Otol Rhinol Laryngol 1925;34:519–527.
8 Harris HL: Anatomy of temporomandibular articulation and adjacent structures. J Am Dent Assoc 1932;19:584–589.
9 Costen JB: A syndrome of ear and sinus symptoms dependent upon disturbed function of the temporomandibular joint. Ann Otol Rhinol Laryngol 1934;43:1–15.
10 Sicher H: Temporomandibular articulation in mandibular overclosure. J Am Dent Assoc 1948;36: 131–139.
11 Zimmerman AA: Evaluation of Costen's syndrome from an anatomic point of view; in Sarnat BG (ed): The Temporomandibular Joint. Springfield, Thomas, 1951, pp 82–110.
12 Block LS: Diagnosis and treatment of disturbances of the temporomandibular joint, especially in relation to vertical dimension. J Am Dent Assoc 1947;34:253–260.
13 Thompson JR: Concepts regarding function of the stomatognathic system. J Am Dent Assoc 1954;48:626–637.
14 Weinberg LA: Role of condylar position in TMJ dysfunction-pain syndrome. J Prosthet Dent 1979;41:636–643.
15 Shore NA: Occlusal Equilibration and Temporomandibular Joint Dysfunction. Philadelphia, Lippincott, 1959.
16 Jarabak JR: An electromyographic analysis of muscular and temporomandibular joint disturbances due to imbalances in occlusion. Angle Orthod 1956;26:170–190.
17 Ramfjord SP: Dysfunctional temporomandibular joint and muscle pain. J Prosthet Dent 1961;11: 353–374.
18 Dawson PE: Temporomandibular joint pain-dysfunction problems can be solved. J Prosthet Dent 1973;29:100–112.
19 Carlsson GE, Droukas B: Dental occlusion and the health of the masticatory system – A literature review. J Craniomandib Pract 1984;2:142–147.
20 Seligman DA, Pullinger AG: The role of functional occlusal relationships in temporomandibular disorders: a review. J Craniomandib Disord Facial Oral Pain 1991;5:265–279.
21 Goodman P, Greene CS, Laskin DM: Response of patients with myofascial pain-dysfunction syndrome to mock equilibration. J Am Dent Assoc 1976;92:755–758.
22 Selye H: The Physiology and Pathology of Exposure to Stress. Montreal, Medical Publications, 1950.
23 Schwartz L: Conclusions of the temporomandibular joint clinic at Columbia. J Periodontol 1958;29:210–212.
24 Laskin DM: Etiology of the pain-dysfunction syndrome. J Am Dent Assoc 1969;79:147–153.
25 Moulton RE: Emotional factors in non-organic temporomandibular joint pain. Dent Clin North Am 1966;10:609–620.
26 Lupton DE: Psychological aspects of temporomandibular joint dysfunction. J Am Dent Assoc 1969;79:131–136.
27 Schwartz RA, Greene CS, Laskin DM: Personality characteristics of patients with myofascial pain-dysfunction (MPD) syndrome unresponsive to conventional therapy. J Dent Res 1979;58: 1435–1439.
28 Rugh JD, Solberg WK: Psychological implications in temporomandibular pain and dysfunction; in Zarb GA, Carlsson GE (eds): Temporomandibular Joint Function and Dysfunction. Copenhagen, Munksgaard, 1979, pp 239–268.

29 Malow RM, Olson RE, Greene CS: Myofascial pain-dysfunction syndrome: a psychophysiological disorder; in Golden C, Alcaparras S, Strider F, Graber B (eds): Applied Techniques in Behavioral Medicine and Medical Psychology. New York, Grune & Stratton, 1981, pp 101–133.
30 Dworkin SF, LeResche L: Research diagnostic criteria for temporomandibular disorders: review, criteria, examination and specifications, critique. J Craniomandib Disord Facial Oral Pain 1992;6:301–355.
31 Greene CS: Focus paper – The etiology of temporomandibular disorders: implications for treatment. J Orofac Pain 2001;15:93–105.
32 Greene CS: Meprobamate therapy for the myofascial pain-dysfunction (MPD) syndrome: a double-blind evaluation. J Am Dent Assoc 1971;85:587–590.
33 Laskin DM, Greene CS: Influence of the doctor-patient relationship on placebo therapy for patients with myofascial pain-dysfunction (MPD) syndrome. J Am Dent Assoc 1972;85:892–894.
34 Magnusson T, Carlsson GE: Treatment of patients with functional disorders in the masticatory system: a survey of 80 consecutive patients. Swed Dent J 1980;4:145–153.
35 Zarb GA, Thompson GW: Assessment of clinical treatment of patients with temporomandibular joint dysfunction. J Prosthet Dent 1970;24:542–554.
36 Greene CS, Markovic M: Response to nonsurgical treatment of patients with positive radiographic findings in the temporomandibular joints. J Oral Surg 1976;34:692–697.
37 Turk DC, Zaki HS, Rudy TE: Effects of intraoral appliances and biofeedback/stress management alone and in combination in treating pain and depression in patients with temporomandibular disorders. J Prosthet Dent 1993;70:158–164.
38 Dworkin SF: Behavioral and educational modalities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:128–133.
39 Dworkin SF, Turner JA, Wilson L, et al: Brief group cognitive-behavioral intervention for temporomandibular disorders. Pain 1994;59:175–187.
40 Okeson JP: Long-term treatment of disk-interference disorders of the temporomandibular joint with anterior repositioning occlusal splints. J Prosthet Dent 1988;60:611–616.
41 Greene CS, Laskin DM: Long-term evaluation of conservative treatment for myofascial pain-dysfunction syndrome. J Am Dent Assoc 1974;89:1365–1368.
42 Cohen SR: Follow-up evaluation of 105 patients with myofascial pain-dysfunction syndrome. J Am Dent Assoc 1978;97:825–828.
43 de Leeuw R, Boering G, Stegenga B, de Bont LG: Symptoms of temporomandibular joint osteoarthrosis and internal derangement 30 years after non-surgical treatment. Cranio 1995;13:81–88.
44 Mjersjö C, Carlsson GE: Long-term results of treatment for temporomandibular joint pain-dysfunction. J Prosthet Dent 1983;49:809–815.
45 Greene CS, Laskin DM: Long-term evaluation of treatment for myofascial pain-dysfunction syndrome: a comparative analysis. J Am Dent Assoc 1983;107:235–238.
46 Mjersjö C, Carlsson GE: Analysis of factors influencing the long-term effects of treatment of TMJ pain-dysfunction. J Oral Rehabil 1984;11:289–297.
47 Okeson JP, Hayes DK: Long-term results of treatment for temporomandibular disorders: an evaluation by patients. J Am Dent Assoc 1986;112:473–478.
48 Greene CS, Laskin DM: Long-term status of clicking in patients with myofascial pain and dysfunction. J Am Dent Assoc 1988;117:461–465.
49 Garafis P, Grigoriadu E, Zarafi A, Koidis PT: Effectiveness of conservative treatment for craniomandibular disorders: a 2-year longitudinal study. J Orofac Pain 1994;8:309–314.
50 Stohler CS, Zarb GA: On the management of temporomandibular disorders: a plea for a low-tech, high-prudence therapeutic approach. J Orofac Pain 1999;13:255–261.
51 Clark GT, Seligman DA, Solberg WK, Pullinger AG: Guidelines for the treatment of temporomandibular disorders. J Craniomandib Disord Facial Oral Pain 1990;4:80–88.
52 Greene CS: Managing TMD patients: initial therapy is the key. J Am Dent Assoc 1992;123:43–45.
53 Bell WE: Orofacial Pains – Differential Diagnosis. Dallas, Denedco of Dallas, 1973.
54 Klasser GD, Greene CS: Predoctoral teaching of temporomandibular disorders: a survey of U.S. and Canadian dental schools. J Am Dent Assoc 2007;138:231–237.
55 Haskin CL, Milam SB, Cameron IL: Pathogenesis of degenerative joint disease in the human temporomandibular joint. Crit Rev Oral Biol Med 1995;6:248–277.

56 Israel HA, Saed-Nejad F, Ratcliffe A: Correlation between arthroscopic diagnosis of osteoarthritis and synovitis of the human temporomandibular joint and keratan sulfate levels in the synovial fluid. J Oral Maxillofac Surg 1997;55:210–217.
57 Mense S: Nociception from skeletal muscle in relation to clinical muscle pain. Pain 1993;54: 241–289.
58 Stohler CS: Muscle-related temporomandibular disorders. J Orofac Pain 1999;13:273–284.
59 Sessle BJ: The neural basis of temporomandibular joint and masticatory muscle pain. J Orofac Pain 1999;13:238–245.
60 Melzack R, Wall PD: Pain mechanisms: a new theory. Science 1965;150:971–979.
61 Feine JS, Lund JP: An assessment of the efficacy of physical therapy and physical modalities for the control of chronic musculoskeletal pain. Pain 1997;71:5–23.
62 Crider AB, Glaros AG: A meta-analysis of EMG biofeedback treatment of temporomandibular disorders. J Orofac Pain 1999;13:29–37.
63 Dao TT, Lavigne GJ, Charbonneau A, Feine JS, Lund JP: The efficacy of oral splints in the treatment of myofascial pain of the jaw muscles: a controlled clinical trial. Pain 1994;56:85–94.
64 Türp JC, Komine F, Hugger A: Efficacy of stabilization splints for the management of patients with masticatory muscle pain: a qualitative systematic review. Clin Oral Invest 2004;8:179–195.
65 Forsell H, Kalso E, Vehmanen R, Puuka P, Alanen P: Occlusal treatments in temporomandibular disorders: a qualitative review of randomized controlled trials. Pain 1999;83:549–560.
66 Aaron LA, Burke MM, Buchwald D: Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med 2000;160:221–227.
67 Korszun A, Papadopolous E, Demitrack M, Engleberg C, Crofford L: The relationship between temporomandibular disorders and stress-associated syndromes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:416–420.
68 de Leeuw R, Klasser GD, Albuquerque RJ: Are female patients with orofacial pain medically compromised? J Am Dent Assoc 2005;136:459–468.
69 Griep EN, Boersma JW, de Kloet ER: Altered reactivity of hypothalamic-pituitary-adrenal axis in the primary fibromyalgia syndrome. J Rheumatol 1993;20:469–473.
70 Tsigos C, Chrousos GP: Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res 2002;53:865–871.
71 Dawson PE: Evaluation, Diagnosis, and Treatment of Occlusal Problems, ed 2. St Louis, Mosby, 1989.
72 Nickerson JW, Veaco NS: Condylotomy in surgery of the temporomandibular joint. Oral Maxillofac Surg Clin North Am 1989;1:303–327.
73 Cooper BC: The role of bioelectronic instrumentation in the documentation and management of temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;83: 91–100.
74 Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D: COMT val-158-met genotype affects μ-opioid neurotransmitter response to a pain stressor. Science 2003;299:1240–1243.
75 Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagan D, Max MB, Makarov SS, Maixner W: Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14:135–143.
76 Schafer M, Carter L, Stein C: Interleukin-1β and corticotropin-releasing factor inhibit pain by releasing opioids from immune cells in inflamed tissue. Proc Natl Acad Sci USA 1994;91: 4219–4223.
77 Dubner R: Neuronal plasticity and pain following peripheral tissue inflammation or nerve injury; in Bond MR, Charlton JE, Woolf CJ (eds): Proc Sixth World Congress on Pain. Amsterdam, Elsevier, 1991, pp 264–276.
78 Sessle BJ: Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. Crit Rev Oral Biol Med 2000;11:57–91.
79 Ren K, Dubner R: Focus paper – Central nervous system plasticity and persistent pain. J Orofac Pain 1999;13:155–163 (see also commentaries by Dionne, Hu and Widmer, pp 164–169).

80 Israel HA, Saed-Nejad F, Ratcliffe A: Correlation between arthroscopic diagnosis of osteoarthritis and synovitis of the human temporomandibular joint and keratan sulfate levels in the synovial fluid. J Oral Maxillofac Surg 1997;55:210–217.
81 Shafer DM, Assael L, White LB, Rossomando EF: Tumor necrosis factor-α as a biochemical marker of pain and outcome in temporomandibular joints with internal derangements. J Oral Maxillofac Surg 1994;52:786–791.
82 Alstergen P, Kopp S: Prostoglandin E_2 in temporomandibular joint synovial fluid and its relation to pain and inflammatory disorders. J Oral Maxillofac Surg 2000;58:180–186.
83 Kubota E, Kubota T, Matsumoto J, Shibata T, Murakami KI: Synovial fluid cytokines and proteinases as markers of temporomandibular joint disease. J Oral Maxillofac Surg 1998;56: 192–198.
84 Ernberg M, Hedenberg-Magnusson B, Alstergen P, Lundeberg T, Kopp S: Pain, allodynia, and serum serotonin levels in orofacial pain of muscular origin. J Orofac Pain 1999;13:56–62.
85 Lund JP: Muscular pain and dysfunction; in Laskin DM, Greene CS, Hylander WL (eds): TMDs: An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006, pp 99–104.
86 Gonzalez YM, Mohl ND: Masticatory muscle pain and dysfunction; in Laskin DM, Greene CS, Hylander WL (eds): TMDs: An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006, pp 255–270.
87 Grossi ML, Goldberg MB, Locker D, Tenenbaum HC: Reduced neuropsychologic measures as predictors of treatment outcome in patients with temporomandibular disorders. J Orofac Pain 2001;15:329–339.
88 Garafolo JP, Gatchel RJ, Wesley L, Ellis E: Predicting chronicity in acute temporomandibular joint disorders using the Research Diagnostic Criteria. J Am Dent Assoc 1998;129:438–447.
89 Crue BL: The present state of therapy for chronic pain states; in Crue BL (ed): Pain: Research and Treatment. New York, Academic Press, 1975.
90 Ohrbach R: Biobehavioral therapy; in Laskin DM, Greene CS, Hylander WL (eds): TMDs: An Evidence-Based Approach to Diagnosis and Treatment. Chicago, Quintessence, 2006, pp 391–402.

Charles S. Greene, DDS
Clinical Professor, Director of Orofacial Pain Studies
Department of Oral Diagnosis and Diagnostic Sciences
University of Illinois at Chicago
College of Dentistry, 801 South Paulina Avenue M/C 838
Chicago, IL 60612–7213 (USA)
Tel. +1 312 413 1069, Fax +1 312 355 2688, E-Mail cgreene@uic.edu

Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007, vol 15, pp 236–247

The End of an Era: Orofacial Pain Enters the Genomic Age

Implications and Opportunities for Research and the Care of Patients

Christian S. Stohler

University of Maryland Dental School, Baltimore, Md., USA

Abstract

With the new century came technologies that provide the ability to measure the response of thousands of genes to experimental stimuli or the development of disease, producing answers in days what previously exceeded a researcher's lifetime to discover. What has changed in the research environment is the persuasive promise that 'out-of-the-box' thinking, enabled by new and powerful biotechnological tools, offers promise to crack the puzzle that underlies the disabling orofacial pain conditions, replacing the 'magic bullet' idea of one treatment to fit all patients with therapies customized to a particular patient's molecular or genomic fingerprint. New thinking endorses that (1) genes constitute risk factors by themselves, (2) they may amplify an existing polygenic risk or (3) they may exacerbate the effect of an environmental risk factor and/or risk-conferring behavior. At first impression, it may appear that adding genotyping to ongoing clinical research protocols will do the trick for clinical research into the etiology, pathogenesis and treatment response of the orofacial pain conditions. However, on closer examination, it becomes clear that the phenotype of all orofacial pain conditions is insufficiently defined in terms of the scope, the natural history and/or clinical course of the disease subgroup of interest, and, most importantly, with respect to disease traits for which laboratory research has provided important pathogenetic insight. How and when the new outlook will come into effect will depend on those that embrace the redefined frontier of orofacial pain.

On October 4, 2006, the X Prize Foundation called for someone to map 100 different human genomes in just 10 days, offering a USD 10 million award. This announcement is supposed to speed up the era of personal genomics, in which an individual's propensity to disease, response to drugs and other health

predilections are individually mapped. Rapid genome sequencing has become an enabling tool that will allow scientists and clinicians to look at diseases in a whole new way. What does this mean for research and the care of orofacial pain conditions, which – on the surface – demonstrate little evidence of a genetic component?

At the Doorstep to the 21st Century

Until about 20 years ago, unicausal explanatory models of disease have shaped the inquiry and clinical practice of orofacial pain conditions, forming the basis for many 'magic-bullet-type' therapeutic interventions that were introduced to the practicing communities over the past 50 years and which still continue to dominate the care spectrum offered today. As an example, for the subject of temporomandibular joint diseases and disorders (TMJDs), the most common orofacial pain conditions, physical factors, such as structural variations in the mandibular condyle-to-glenoid-fossa relationship, the dental occlusion or the alignment of the articular disk in relation to the mandibular condyle at rest and during function were believed to exert causal effects, sufficient to result in the generation of symptoms and signs that are viewed as the core features of the TMJDs. In addition, nonspecific stress was implicated as the cause of bruxism, which in turn was regarded as a significant factor in the onset of the TMJDs.

In other words, simple structural and/or behavioral explanations of disease causation were widely endorsed because alterations of the presumed cause by a range of therapeutic interventions, addressing presumably relevant structural variations or behavioral issues, resulted in the alleviation of the clinical hallmark features of the TMJDs in many cases. The fact that the prevailing therapeutic interventions involve mechanical acts that represent 'the bread and butter' of surgical disciplines must also be viewed as reason for the popularity and acceptance of those explanatory models. Because of the very fact that the respective interventions impressed providers and patients by their intuitive appeal, the alleviation of the patient's symptoms seemed to confirm the causal assumption that justified the rendered intervention in the first place (fig. 1).

The fact that early clinical research focusing on the orofacial pain conditions rarely included controls as contrasts bothered few authors and clinicians. Consequently, the search for alternative explanatory models of causation only appeared after it became clear that many interventions proved to be no different from a credible placebo with respect to the effect of the intervention on disease-defining indicators over the course of application. For example, regarding occlusal appliances, devices widely used for the management of TMJDs and assumed to produce beneficial effects via the induction of physical changes of

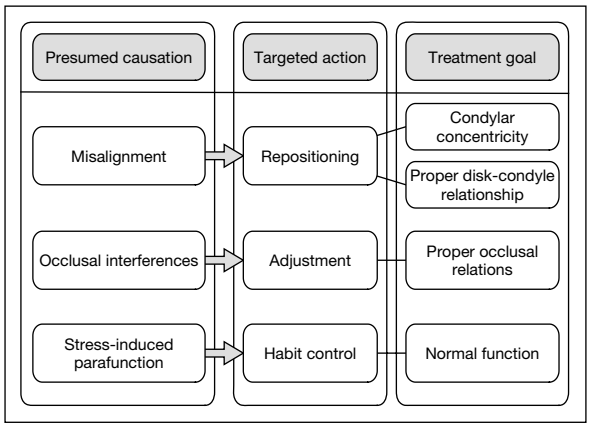

Fig. 1. Structural and behavioral explanations of TMJD causation, clinical actions aimed at the presumed causation and expected treatment goal (see text).

the dental occlusion, a critical review of the literature reveals that their efficacy is in actuality not better than a credible placebo therapy [1].

New Tools, New Thinking

As the original literature, notably introductions and discussions of papers, is shaped by the prevailing thinking of disease causation, the findings of a particular piece of research largely escaped alternative interpretation. Why should it, as the prevailing thinking of the time defined the research question in the first place, endorsing a state of certainty that was not based on sound scientific methodology? Although the scientific method began to influence larger and larger fields of study in the second half of the 20th century, there was little opportunity for 'out-of-the-box' thinking in the field of orofacial pain until the early nineties because the research questions and care delivery were largely articulated within the prevailing beliefs of the time. In general, it is not until a discipline or field of study redefines the conceptual framework within which the clinical phenomenology is understood and managed that the nature of the research questions changes and a re-interpretation of the original literature will occur.

Today, it is my belief that the time for a new beginning of the research and the clinical thinking of the subject of orofacial pain has come. With the new century arrived, technologies that provide the ability to measure the response of thousands of genes to experimental stimuli or the development of disease

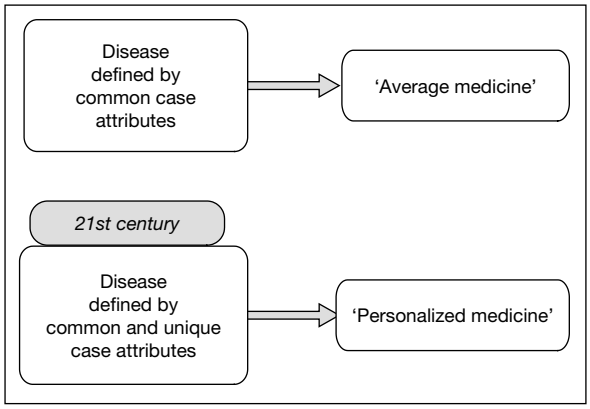

Fig. 2. Average versus personalized medicine.

produce answers in days what previously exceeded a researcher's lifetime to comprehend. At the doorstep to the 21st century, biotechnology, notably rapid global genotyping, changed the toolbox and outlook of clinical scientists that previously embraced narrowly defined research questions and disease descriptions using the least common denominator for case delineation for which average response characteristics were subsequently computed.

With the turn of the century, the subject of orofacial pain has become no different from many other intricate diseases, such as osteoporosis, adult diabetes or hypertension that proved to be far more complex than was assumed previously. While prior analytical efforts focused on establishing rules for patient averages, the wide range of symptom expression, including the presence of comorbid conditions, notably in those patients that exhibited the greatest treatment need, had to be overlooked for analytical reasons so that average response characteristics for a narrowly shared common disease trait or pattern of traits could be derived. However, rather than depending upon average disease descriptions, the 21st century discovery toolbox, genome sequencing, requires the valid measurement of individually unique disease attributes in its broadest context because knowledge of their case-specific expression is essential for meaningful linkages with the molecular pathways and controlling genes that confer the respective tissue-specific vulnerability (fig. 2).

Diagnostic classification systems, focusing on a limited number of clinical features, abandoning signs and symptoms outside the strict topographical domain of interest, are not suited for the study of complex diseases in which environmental factors, risk-conferring behaviors and many genes are at work to produce the unique clinical presentation encountered in a given patient. The

challenge will be to understand the interactions between genes, genes and hormones and/or cytokines, and between genes and environmental risk factors (or vice versa) that underlie the development of a particular disease trait, such as a distinct sign and/or symptom linked to conditions of orofacial pain. The fact that the literature defines the phenotype often in narrow terms, limiting the description to a set of site-specific traits within a tight topographical domain, will pose a challenge when translating past knowledge into the conceptual 21st century framework of a complex disease. This underscores the point made earlier that the time for a new beginning has come, since average response descriptions of orofacial pain conditions and individual vulnerability and/or individualized therapy, also referred to as personalized medicine, cannot be consolidated, no matter how serious the effort may be. Only quality contributions of the original literature over the past 10 years or more can likely be used as the foundation for the new beginning.

While the limitations of the clinical knowledge base should be apparent, lessons learned from the experimental literature relevant to orofacial pain conditions hold promise for advancing our existing disease classification schemes. This body of literature offers cues to molecular pathways and risk-conferring exposures that shape discrete aspects of the complex phenotypes observed in clinics. As such, experimental models represent abstractions that capture isolated aspects of the complex system in effect clinically. However, the field is far from understanding the extent to which and when particular basic mechanisms or scenarios observed in experimental model systems are of significance to an individual case in the clinic. In addition, genetic manipulations in the laboratory have only produced few attributes that mimic a limited set of disease traits found clinically. Nonetheless, this knowledge base offers a great start for a new beginning.

Where do we go from here? At this point, it should be apparent that research using experimental model systems and inquiries involving human patients can no longer occur in isolation. These previously minimally coordinated lines of research will require unprecedented cross-talk, not at the level of data exchange in the publication format but in the discovery phase through meaningful interaction between basic and clinical scientists. The need for parallel (a) molecular/gene expression tissue profiling, and (b) both valid and comparable phenotyping of clinic cases and experimental models must be apparent because such contrasts provide insight into the significance of an experimental model for the disease of interest and the conditions under which the model system has relevance to a particular clinical scenario. The hunt is on for signature genes, i.e. those genes that are either significantly up- or downregulated with respect to background measurements, to arrive at a plausible molecular explanation for the disease traits in question. Bottom-up science directed from bench

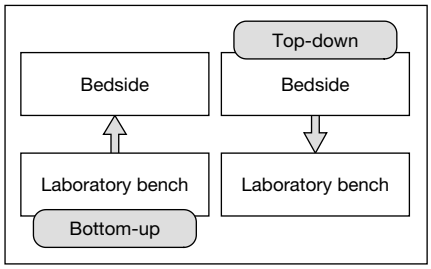

Fig. 3. Bottom-up and top-down discovery.

to clinic, and top-down science, moving the discovery from the clinic to the laboratory bench have to work in a concerted fashion (fig. 3).

A small research team with restricted research focus, expertise and/or skill set will increasingly face difficulty in competing successfully in this emerging paradigm of bidirectionally ('bottom-up/top-down') coordinated discovery, having obvious limitations without broadening the scope of research questions and interactions with experts outside the immediate field of inquiry. The idea of a 'magic bullet' or 'one-fits-all' therapy, harvesting the regulatory influence of a single molecular target to cure complex diseases, is conceptually more distant than it ever has been. This is also the case for the TMJDs, where individually expressed genetic vulnerabilities, environmental factors and risk-conferring behaviors shape the individual disease expression and treatment response. Understanding the complex disease-generating biological machinery has become as important as knowledge of the individual, regulatory effects of a particular molecular target in an experimental model system that purposely restricts its system complexity.

A Challenging Phenotype

Currently, the presence or absence of a few signs and symptoms within a narrow topographical domain define the disease state, which – for example in the best-case scenario of the Research Diagnostic Criteria for TMJDs (RDC/TMD) – is described by an operationally specified standard, ensuring reliable case delineation to diagnostic subsets by adhering to strict assignment rules [2]. Earlier taxonomies are much more challenging in this respect as the validity of the case assignment is not defined by a disease threshold stated in operational terms, let alone one that is biologically both valid and plausible [3].

At first impression, it may appear that adding genotyping to promising clinical research protocols incorporating valid phenotyping using current

taxonomies will do the trick for clinical research into the etiology, pathogenesis and treatment response of the orofacial pain conditions. However, on closer examination, it becomes clear that the phenotype of all orofacial pain conditions is insufficiently characterized in terms of (1) the variability of expression both interindividually and intraindividually, (2) the natural history and/or clinical course, (3) the response to treatment and/or pharmacological challenges, and (4) most importantly, with respect to disease traits for which laboratory research has provided pathogenetic insight. Although often overlooked, it must be understood that for allelic association studies, valid and biologically plausible phenotype delineation is as important as the validity of the genotyping process. Progress in identifying alleles that are either important causally or confer vulnerability will not be achieved without significant advances in characterizing the clinical material. This seems to be a matter that is getting insufficient consideration both in peer reviews and by funding agencies at this time. In the case of the RDC/TMD, it is striking that the predictive power of axis I with respect to disease progression or treatment response is glaringly absent after more than 10 years of research. Consequently, there is little hope that a particular gene or genes can be linked to subsets that are defined in anatomical terms, i.e. muscle, articular disk, joint.

Because of the nature of information captured by current taxonomies for the orofacial pain conditions, notably for the TMJDs, phenotype-genotype association studies will be challenging. Cases are identified by a recognizable pattern of clinical features within a particular anatomical domain, which occur together more frequently than expected by chance. While anatomical classification systems, e.g. pain conditions involving muscle, joint or the articular disk of the temporomandibular joint, are appealing in support of a rule-based management of symptom complexes within a topographical domain (although evidence in support of this claim is lacking), such taxonomic systems appear to contain insufficient physiological and/or biochemical detail to classify cases according to pathogenetic mechanisms, which in turn constitutes a necessity for associating clinically observable 'functional' phenomena with genotypes. Although signs and symptoms appear to run together, the possibility of causal heterogeneity is more likely than not. Unlike for many psychiatric diseases for which current classification schemes contain some 'functional' criteria for case assignment, it is only the axis II of the RDC/TMD taxonomy that – although lacking specificity with respect to the site within which symptoms are reported – contains measures with inherent predictive power [2].

At first sight, anatomical systems are appealing because they guide the treating (surgery-oriented) clinician to a specific peripheral tissue that appears to be in need of being addressed therapeutically. However, if one considers the idea that the pain condition is explained by a model of disease in which

regulatory processes increase the expression of symptoms in a vulnerable body part and if we acknowledge that the diagnostic label for a particular subtype of disease, assigned to a specific case, is not stable over time, the question arises as to what good does an anatomical focus offer. The problem of the current anatomical focus is also exemplified by the fact that cytogenetics is not an option for the TMJDs nor any of their anatomically defined subsets because it is not known which cells of which particular tissue should be harvested for analysis.

Given the current state of phenotyping of the orofacial pain conditions, putative linkages identified in one study may not be confirmed in replication work, particularly if the threshold of disease, the subject's predisposition beyond as set value, is different among studies. With respect to the repeated confirmation of an allelic association, issues related to the validation of protocols and reagents, or differences between microarray platforms of different manufacturers, i.e. validity of cross-platform comparisons of gene expression data, may also lead to disagreement between association studies as well. In sum, groundwork is still needed on all fronts for the field to take advantage of the powerful tools available today.

Genetic Risk Models

On careful inspection, advancing the research and care of the orofacial pain conditions, tackling the mechanisms of their genetic control is more challenging than commonly assumed. For TMJDs as an example, their etiology is unknown, the clinical course appears to be nonprogressive, the prevalence is higher during the reproductive years in both genders, and although the female gender as well as head trauma are established to favor disease risk, their effect size is insufficiently large to explain causation. In fact, the effect size is modest at best. Furthermore, the genetic contribution to the disease is not obvious based on observations in the clinic.

Given this background, any valid genetic risk model has to fit the assumptions underlying the known distribution of disease as specified above. Consequently, it appears that TMJDs are not adequately explained by a single gene but it can be stated that the disease state is mediated by sex-genotype-dependent susceptibility, derived from the interactions of multiple genes. In addition, there is the real possibility that genes influence (1) the clinical heterogeneity within disease classes and (2) the extent to which putative environmental factors and risk-conferring behaviors exert their effect.

As genetic models are only meaningful when the best estimates of the disease distribution are in agreement, a multifactorial etiology should be assumed for the TMJDs because the disorder is clearly a greater issue for the female

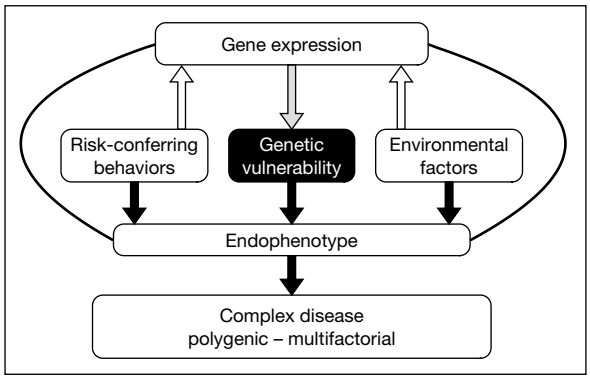

Fig. 4. Pathogenetic model of disease causation, acknowledging the multifactorial etiology and polygenic vulnerability in the context of the subject-specific endophenotype and gene expression.

gender – both in terms of prevalence and severity of the state of disease. From a genetic modeling perspective, multiple genes should be postulated to interact with environmental factors, not much different from Alzheimer disease, diabetes, many psychiatric disorders, parkinsonism or cardiovascular diseases, including stroke. Genes may (1) constitute risk factors by themselves, (2) amplify an existing polygenic risk or (3) exacerbate the effect of an environmental risk factor or risk-conferring behavior. Furthermore, these effects are expressed in the context of a particular endophenotype whose overall system response is shaped by genes and acquired response behaviors (fig. 4).

As mentioned, disease susceptibility is founded on either the additive or multiplicative effect of multiple genes that together with environmental exposures, including the effect of risk-conferring behaviors, form the basis for a particular disease trait that is encountered with significant likelihood – different from random occurrence – in those carrying the genes in question. In other words, the distribution of the TMJDs – again as an example – suggests that it is not the mutation of a single gene that leads to the disease phenotype. Instead, the risk of getting the disease/disorder is significantly greater if certain polygenic conditions are present, while the rate and time for developing the disease phenotype seem to be influenced by factors such as age and gender, among other less well-established environmental factors and risk behaviors. This thinking of the actions of genes in diseases of multifactorial etiology was not entertained when most of us were introduced to the principles of genetics, studying models of mendelian inheritance; however, it will increasingly define the road map for future research and care.

The Challenge of Cracking the Puzzle

Besides issues with the limited scope of case characterization and the phenotype delineation according to pathogenetic significance, the next generation of clinical research of the orofacial pain conditions faces other, equally challenging hurdles. Not only will the research design have to fit the genetic model of the disease, but the question needs to be entertained as to how many subjects should be included in an allelic association study so that the work is not underpowered. Should the inclusion of subjects be restricted to a specific ethnic background, because otherwise the discovery of genes and influencing environmental factors is clouded by noise linked to differences in ancestry, notably if the contribution of a candidate allele to the phenotypic trait is mild to modest? If so, how will the restriction of the research endeavor to a particular ethnic subpopulation be justified to a funding agency? If not, complicated analyses are in order to control for differences in ancestry. Although large-scale testing is preferred, the more cases the better, how many allelic associations with phenotypic traits – as identified by microarray technologies – can be validly explored, assuming that 5% of associations will be statistically significant by chance alone?

While the conceptual framework and software tools to estimate sample sizes for clinical research projects are in place for genetic analyses using mendelian inheritance models, computing the number of subjects required to ensure validity of research into complex diseases, including the orofacial pain conditions, is not easily ascertained. In fact, how can it be as the underlying genetic model of disease is the research question in itself? Assuming a dichotomous case delineation, i.e. the phenotypic trait is either present or not, what are the implications of the chosen threshold level that constitutes liability for the development of the sign or symptom in question on the required sample size? Alternatively, if a trait is characterized in quantitative terms, i.e. sensitivity to pain, how large does the study population have to be to capture the interaction of many genes that all have a minor effect individually, but in combination may explain a moderate, yet significant portion of the risk of developing the particular disease trait? Moving forward, particularly in the context of funded research, means having answers to the research questions that are subject to being answered by the very same research. Clearly, this is not a good outlook to promise rapid progress.

It should also be obvious that the pool of talent that shaped the research agenda and produced the advances of the field of orofacial pain has come to a point where both the narrowly defined scientific and clinical expertise of the investigators and the limited scope in phenotyping of clinic cases are stifling progress. It should be noted, however, that the phenotype characterization that

was implemented in the nineties is not all bad because some marker alleles seem to be statistically linked to the disease as defined by the expanded features of current diagnostic grids, such as those related to affect [4].

Although the possibility of allelic association studies, covering the whole genome, has become a reality, the excitement needs to be dampened by the fact that advances in genetic epidemiology – notably the need for relevant phenotyping, such as (a) identifying individual variations in clinically observable signs and symptoms, (b) the level of expression of potentially significant biomarkers, (c) functional brain and endophenotypical response patterns to experimental stressors and pharmacological challenges or (d) the magnitude of the perceptions induced in response to stressful life events – are needed to arrive at more homogenous subgroups, reducing the already overwhelming complexity of the research question at hand. While the exposure to particular life events has been associated with risk for certain types of persistent pain, it has to be kept in mind that the magnitude of the perceptual response induced by a stressful life situation has a genetic basis as well. The ultimate question will arise with respect to the specificity of any allelic association when it comes to its manifestation in the trigeminal system, as – for example – the axis I of the RDC/TMD has little predictive power while axis II criteria capture pain response measures that have limited specificity for the topographical domain within which the disease/disorder manifests itself. At present, significant allelic associations with individual response phenotypes are limited to case attributes that are contained in the expanded scope of axis II of the RDC/TMD, particularly functional pain response measures [5, 6].

Conclusions

What has changed in the research environment is the persuasive promise that 'out-of-the-box' thinking, enabled by new and powerful biotechnological tools, offers great promise to crack the puzzle that underlies the disabling orofacial pain conditions. However, 21st century science has become as complex as the diseases that are being studied. How and when the new outlook will dominate the research thrust geared to disentangle the complexities of the orofacial pain conditions will depend on those that embrace the redefined frontier of orofacial pain, leveraging the opportunities in collaborative efforts that are waiting to be mined. Although the speed by which the new tools offer insight is unprecedented, it is not going to happen if business continues to be as usual. To enter the genomic era, a real change in the mindset of those involved in studying and treating orofacial pain diseases and disorders is required.

References

1 Kreiner M, Betancor E, Clark GT: Occlusal stabilization appliances: evidence of their efficacy. J Am Dent Assoc 2001;132:770–777.

2 Dworkin SF, LeResche L: Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord Facial Oral Pain 1992;6: 301–355.

3 Ohrbach R, Stohler CS: Current diagnostic systems. J Craniomandib Disord Facial Oral Pain 1992;6:307–317.

4 Palyo SA, Beck JG: Post-traumatic stress disorder symptoms, pain, and perceived life control: associations with psychosocial and physical functioning. Pain 2005;117:121–127.

5 Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D: COMT val158met genotype affects μ-opioid neurotransmitter responses to a pain stressor. Science 2003;299:1240–1243.

6 Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagin D, Max MB, Makarov SS, Maixner W: Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14:135–143.

Christian S. Stohler, DDS, Dr. Med. Dent.
Professor and Dean
University of Maryland Dental School
650 W Baltimore Street
Baltimore, MD 21201 (USA)
Tel. +1 410 706 7461, Fax +1 410 706 0406, E-Mail cstohler@umaryland.edu

Author Index

Subject Index