Chronic Orofacial Pain: Is the Puzzle Unraveling?

Christian S. Stohler, D.D.S.

Abstract: Conditions involving chronic orofacial pain represent a major health problem, and patients with persistent pain are difficult to manage successfully. These conditions are often comorbid with additional health issues such as sleep disturbances, cardiovascular, gastrointestinal and reproductive system complaints, weight loss or weight gain, swelling, numbness, sweating and flushing, and concerns regarding loss of libido, drive, attention, and memory. Neuroendocrine and autonomic pain-stress responsivity and the consequences of pain for sensory, motor, immune and reproductive functions, and mood seem to account for the broad range of comorbid complaints. Susceptibility to a particular response appears to explain intra-individual differences in disease expression. Understanding of these regulatory, mostly adaptive processes will support novel treatments to manage many troublesome comorbid complaints for which current approaches are unsatisfactory.

Dr. Stohler is William R. Mann Professor and Chair of the Department of Biologic and Material Sciences, University of Michigan School of Dentistry. Direct correspondence to him at the Department of Biologic and Materials Sciences, School of Dentistry, The University of Michigan, Ann Arbor, MI 48109-1078; csto@umich.edu.

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Converging evidence from diverse fields of science points to pathogenetic mechanisms, some of which seem to contribute in significant ways to the clinical picture encountered in chronic orofacial pain conditions. Although it remains uncertain whether and exactly how these mechanisms play a role in the persistence of signs and symptoms, there is no question that the experience of pain has consequences for sensory, cognitive, affective, immune, motor, autonomic and reproductive functions, and that some of the effects are either the direct result of pain or a consequence of the activation of the body’s stress-response system.

Overall, unraveling the puzzle produces a fascination with the emerging understanding of a “new” disease. Twenty-first century investigators, clinicians, and patients are forming partnerships that reflect societal values and patients’ preferences, shaping the intellectual framework in support of new diagnostic and therapeutic strategies. I foresee exciting developments in the next two decades in which scientific discovery will provide fundamental understanding that will lead to improved management options, novel treatments, and eventually “cures.” Scientific progress is accelerated by the availability of modern biotechnologies that provide mechanistic understanding of unmatched analytical specificity.

Problematic Scope of Practice

Considerable confusion exists in explaining the basis of many ill-defined, notably chronic diseases and disorders. Regarding chronic orofacial pain, the dental practitioner is often in the midst of such controversy. The confusion is compounded by studies that employ very different criteria for case inclusion and, not surprisingly, often reach opposite conclusions. Because the concerned disciplines encourage a limited scope of practice, information from diverse fields of study is not easily integrated. In this respect, the chronic orofacial pain conditions are no exception.

Shared case features within a single anatomical domain (e.g., the orofacial complex) support diagnostic taxonomies and ease communication among concerned clinicians. While being biased towards case attributes that are “essential” for diagnosis, information regarding comorbid conditions that are observed outside the region of interest is often underrepresented. In fact, clinical attributes that are not essential criteria of the employed diagnostic taxonomy are easily discarded. For example, masticatory myofascial pain, a diagnostic subset of the group of conditions referred to as temporomandibular disorders (TMD), is not always limited to a single topographical domain, yet findings outside the primary region of interest are often missed. In reality, however, chronic TMD pain is associated with comorbid pain conditions in body parts other than the face at much greater rates than the condition is limited to the face.

The alternative view, such as systemic disease affecting the region of interest, needs to be considered as well. For example, fibromyalgia, a clinical disorder that is characterized by pain on left and right sides of the body and pain above and below the waist for at least three months and tenderness to two kilo-
grams of pressure at eleven of eighteen anatomically predefined body sites, can also affect the muscles of mastication in ways that such cases meet the diagnostic criteria of TMD. As far as the relationship between fibromyalgia and TMD is concerned, recent studies performed in academic research/referral centers have shown significant overlap between the two conditions. According to Plesh and coworkers, 75 percent of fibromyalgia patients had TMD while, on the other hand, 18 percent of cases with TMD met the diagnostic criteria for fibromyalgia. Epidemiological studies also report a high association between TMD and the two most common types of headache—tension-type headache and migraine headache. Figure 1 exemplifies the high frequency of pain complaints involving the back of the head, neck, and upper back among tertiary care patients whose orofacial pain was primarily of muscular origin.

Even though average case presentations and mean treatment effects shape much of our clinical actions, the dismissal of individual variation and/or data beyond the immediate scope of practice limit scientific progress. In fact, variation in the extent to which individual symptoms are expressed becomes the center of focus of those concerned with the molecular/genetic basis of phenotypes that are relevant to chronic orofacial pain. Such variations include sleep disturbances, cardiovascular and gastrointestinal complaints, weight loss or weight gain, loss of libido and drive, swelling, numbness, sweating and flushing, and complaints regarding attention and memory. There is a need to broaden the scope of inquiry beyond the common clinical features that consist of 1) limited range of mandibular motion, 2) jaw muscle/joint palpation scores, and 3) factors related to TMJ function, notably articular noises.

**Pathobiological Case Delineation**

Scientific advances are bound to sensible descriptions of the disease. Progress to improve the taxonomies of chronic orofacial pain conditions has been slow, with the exception of the musculoskeletal pain conditions, referred to as TMD or “TMJ.” Concerning TMD, the development of a diagnostic classification system for the major TMD subtypes, headed by the University of Washington’s Pain Research Group and widely referred to as the Research Diagnostic Criteria for TMD (RDC/TMD), was important. Evidence-based and, in cases of insufficient data, complemented by experts’ consensus, the RDC/TMD system permits the classification of major TMD subtypes, allows assignment of several diagnoses to a single case, exhibits features that are useful for epidemiological description and research, and demonstrates features that can be useful to the inexperienced practitioner in defining the care-setting requirements of a particular patient.

Unlike other TMD classification systems, the RDC/TMD taxonomy employs not one but two diagnostic axes. **Axis I** distinguishes three major diagnostic categories: Group I, masticatory myofascial pain; Group II, TMJ internal derangements; and Group III, TMJ arthritides. **Axis II** criteria assess pain intensity, pain-related disability, and emotional symptoms. Application of this dual-axes diagnostic system has solidified the understanding that more than one Axis I diagnosis is often applicable in a given case, that Axis I conditions are not necessarily stable over time, and that significant variation exists with respect to Axis II findings, even within a given Axis I diagnostic subset.

In general, individuals are not equally susceptible to disease. Understanding of the extent to which genetic and epigenetic factors
contribute to susceptibility and vulnerability plays an increasing role in clinical practice. Genetic susceptibility is not limited to increased familial risk of disease, but can involve susceptibility to a particular clinical course of the disease and/or altered responsivity to treatment, including the development of complications. Different genotypes also vary in their response to environmental challenges. In fact, it should be understood that genes not only control metabolic processes but also the response to neurogenic, somatic, and psychogenic stressors, including environmental challenges.

In many, but not all of the studies conducted up to the late 1980s, the validity of findings is in question because the understanding at that time was hampered by limited validity and reliability of case assignment, a situation that continues to be an issue even with current diagnostic systems, although to a lesser degree. If the study sample is invalid, risk assessments derived from those observations are likely also to be invalid.

Problems with case ascertainment continue to be an issue in recent publication. For example, genetic analyses using cases, identified by simple TMD signs and/or symptoms, are unlikely to prove or disprove inheritance in twin studies given the low specificity of the case-defining features. Features that appear as “true” TMD signs and symptoms can be part of normality or be related to conditions mimicking TMD, previous TMD disease, or ongoing, “true” TMD disease. If the qualitative trait in question insufficiently correlates with the presence or absence of disease in the first place, answers with respect to genetic influences on disease and/or the mode of inheritance cannot be expected from studies of familial aggregation.

Diagnostic validity, key to advancing understanding and not an all-or-none issue, pertains to the degree to which study cases share an underlying biological mechanism, and that the criteria used in support of the diagnostic assignment are predictive of some aspect of this common underlying biology. Negative results reported by simple twin/familial aggregation studies should also not be overstated because more plausible genetic models, such as the possibility that the penetrance of susceptibility genes is modulated by polygenic inheritance of deficiencies in pain-stress responsivity, cannot be examined with this approach.

### Autonomic and Neuroendocrine Pain-Stress Response

Complex neuroendocrine and autonomic mechanisms influence any stress-induced deviation from homeostasis with the hypothalamus, in part an endocrine organ and in part a nervous tissue, forming a link between the central nervous system, the supraspinal autonomic reflex centers, and the hypothalamic-pituitary-adrenal (HPA) axis. Initial pain signals a “warning” to the subject to stop the activity provoking it and to take action to escape and alleviate pain. This initial stage is characterized by increased alertness, focused attention, the suppression of feeding, sleep, and reproduction and increased vascular tone, respiration, and gluconeogenesis. If pain is sustained, longer-lasting effects on neuronal excitability (e.g., upregulation of NMDA mediated effects) and even changes in the central nervous system’s “circuitry” occur via a series of effects involving altered gene expression. Binding of c-fos and c-jun to DNA is implicated in the alteration of the transcription of late effector genes, affecting enzymes, growth factors, peptides, and even the phenotype. There is increasing evidence that the transition between initial “warning” and subsequent stages of pain occur within minutes to hours as opposed to days, weeks, or even months. Rather than being based on a biological fact, the idea that it requires six months for pain to be labeled as “chronic” seems to be based on the impression that it takes about 180 days to find out that none of the treatments for the control of pain are satisfactory.

Pain-stress response systems such as the sympathetic nervous system, HPA-axis, and antinociceptive networks support adaptive strategies that allow reasonable function in the presence of persistent pain. Emotional and cognitive neural networks influence the hypothalamic neurosecretory cells that regulate the release of neurohormones (e.g., corticotropin releasing hormone, CRH), which in turn affect hormone synthesis by the pituitary gland (Figure 2). Prolonged exposure to hormonal shifts due to chronic pain-stressors may in some body locations favor adaptive physiological and behavioral responses.
while other locations, both centrally and peripherally, pathological outcomes may arise. Indeed, selected CNS sites have been termed “vulnerable” because of their high density of glucocorticoid receptors, which, when activated in prolonged and/or massive stress, cause long-term changes in dendritic structure, such as in hippocampal regions. \(^{21}\) Neuroplasticity, the process by which the CNS incorporates morphological and/or physiological modification in cell-to-cell communication, is precipitated by repeated stress and hormonal tides. This process seems to explain many of the comorbid conditions associated with chronic pain.

Virtually all of a brain’s functions are modifiable by experience. The process of neuroplasticity permits the incorporation of previous experience into adaptive responses, such as the learned appraisal of stressors modifying the activation of the HPA-axis and sympathetic nervous system in response to a challenge. Recent data point to the effect of previous stressful experiences on subsequent response behavior later in life. For example, lifelong changes in the hippocampal and amygdalar corticoid receptor profiles and function of the HPA-axis have been documented in the context of neonatal and perinatal stressors. \(^{22-26}\) Altered responsivity of adult rats to noxious stimuli have even been observed in animals in which neonatal tissue was subject to experimentally induced persistent hind paw inflammation. \(^{27}\)

Another example, pointing to the effect of previous experience, includes the finding that the type of postnatal handling of Long-Evans rats permanently alters the neurobiological function of the HPA-axis. \(^{28}\) Manipulation of the environment early in life also produces long-lasting modifications of noradrenergic transmission. \(^{29}\) Even social factors exert a lasting impact on stress responsivity as demonstrated by communal status influencing adrenocortical profiles in wild baboons. \(^{25}\) Overall, there is reason to believe that both altered neuronal properties and the reassignment of neurons from one circuit to another result in new properties that are both “good” and “bad,” depending on the circumstances.

### Pain-Stress and Cytokine Signaling

Stressors also influence the immune system. Because the immune system is mostly viewed as a stand-alone structure, its role in chronic pain conditions is not receiving the kind of attention it should. However, the system receives neural and endocrine signals and releases messages, including cytokines that have behavioral consequences \(^{30}\) (Figure 3). Immune-competent cells express receptors for hormones, neurotransmitters, and neuropeptides, with receptor expression varying among the different cell populations. \(^{31}\) Research using model systems has also established that immune-competent cells themselves secrete substances, including many hormones, that not only affect their function beyond the local milieu but also exert effects on central and peripheral targets as well. Cytokines released from immune-competent cells, most notably interleukin-1 (IL-1), directly or indirectly via de novo synthesis in the CNS, affect central neural networks committed to neuroendocrine and autonomic functions. \(^{32}\) Although it is still debated whether peripheral IL-1 crosses the blood-brain barrier, alternative pathways mediate immunologic messages to CNS sites involved in shaping the response to pain. For example, subdiaphragmatic vagotomy in rats prevents or attenuates many of the physiological and behavioral responses...
Overall, it is increasingly recognized that cytokines, acting on central targets, cause sensitization in the sense that subsequent challenges produce augmented responses, including glucocorticoid secretion.

**Pain and Mood**

The worst outcome associated with suffering persistent orofacial pain constitutes dysfunctional chronic pain. Mood alterations are not surprising given that chronic, nonmalignant pain is coupled with the lowest health-related quality of life observed for any medical condition. Fear, anger, tension, worry, frustration, irritability, and sadness are the most prevalent negative mood types that are linked to chronic and severe pain. For the most part, clinical data report on the level of association between disease and particular psychological traits. Given the nature of such data, no conclusions should be drawn regarding cause and effect. Although some investigators have modeled psychological and/or behavioral traits as explanatory factors of the worst outcome, the alternative and more likely conclusion, such as TMD and its treatment causing psychological, cognitive, and behavioral sequelae, are equally supported by data of statistical association.

Besides sensory elements, unpleasantness constitutes an integral part of the pain experience. In the CNS, spatially distinct neural processing of nociceptive input causes arousal in the brain stem and launches affective and cognitive processes in subcortical and cortical regions. This is relevant because treatments seem to exert differential effects on specific aspects of pain. A classic example is the differential treatment effects of diazepam, significantly reducing the affective component of pain while leaving the sensory experience unchanged. Response differences can also be attributed to contextual factors. For example, affective but not sensory pain ratings are lower when women in labor focus attention on birth of the child as opposed to their pain. Our most recent data show that pain-affect is indirectly influenced by the degree to which individual subjects activate the mu-opioid system in spatially discrete CNS locations, pointing again to mechanisms that explain individual vulnerability.

**Pain and Other Sensory Systems**

There is increasing evidence that the processing of noxious and nonnoxious stimuli varies among pain conditions. Although the lowered pressure-pain threshold is a well-established diagnostic criterion of TMD, myofascial pain, and fibromyalgia, there is evidence to suggest that other sensory experiences, such as the response to low-threshold mechanical stimuli, differ between a range of clinical and experimental pain states. For example, clinic cases of TMD pain with a prominent myalgic component demonstrate an elevated vibrotactile threshold in the face. Similarly, patients suffering from chronic cervicobrachialgia exhibit significantly higher detection thresholds for light touch in cervical dermatomes. Unlike capsaicin, experimental heat pain and saline-induced jaw muscle pain similarly affect...

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Figure 3. Diagrammatic representation of the interconnections between the nervous, endocrine, and immune systems. Shaded areas represent painful body sites.
cutaneous low-threshold mechanosensitivity. Because the response characteristics to cutaneously applied noxious mechanical stimuli are indistinguishable between wild-type and VR1-null mutant mice that do not express the receptor targeted by vanilloids, including capsaicin, measurement of low-threshold mechanosensitivity with respect to normoesthesia, hyperesthesia, and hypoesthesia may prove useful in gaining additional mechanistic information of clinic cases beyond the measurement of the pressure-pain threshold (Table 1).

**Pain and Motor Function**

Pain also has direct effects on motor function that include changes in facial expression and body posture, along with a tendency to avoid movements or to execute them more slowly. In addition, pain lowers the ability to work against heavy loads. Among the many effects of pain on motor activity, current taxonomies limit their focus on the impaired range of motion caused by pain.

General motor effects also include the special facial expressions and breathing patterns that accompany pain. Regarding the body part in pain, heavy pressure on the periosteum of the zygoma, for example, reduces the frequency, amplitude, and velocity of mastication initiated by electrical stimulation of the corticobulbar tracts of decerebrate rabbits. Similar effects occur in painful mastication in humans. Voluntary mouth opening is reduced because motor units of jaw closers fire in greater numbers and at higher frequency during painful jaw opening than in the absence of pain. Pain effects on mandibular posture seem to explain the patient’s observation of “teeth not fitting together properly,” a perception that is no longer noticed following the resolution of pain. Contrary to common assumptions, electromyographic data do not support the idea of jaw muscle hyperactivity and spasms at rest (in the overwhelming case majority), and much of the changes in pain, captured by surface electromyography of the jaw musculature, reflect changes in facial expressions caused by pain. Taken together, the inability to contract muscles forcefully and rapidly seems to reduce the risk of further damage to the body, while the typical facial expressions and gestures of pain are indicators to others that the person is in pain, is suffering, and is in need of help and sympathy (Figure 4).

**Pain and the Reproductive System**

Sustained pain appears to affect the reproductive axis as well. When comparing fecundity rates among myofascial face pain patients and demographically equivalent female acquaintance controls, myalgia cases have significantly fewer children and are more likely to have never been pregnant. Indeed, it is highly probable that chronic pain, including facial pain, has a negative effect on the hypothalamic-gonadal axis.

For intact reproductive function, the GnRH pulse generator is critical, because only narrow variations in secretory pulsatility are acceptable for producing normal menstrual cycles. Luteinizing hormone (LH) is released in a pulsatile fashion from the anterior pituitary in response to GnRH. LH pulses, in turn, modulate ovarian steroidogenesis. Although considerable variability both between and within individuals exists, characteristic LH pulse mean frequencies and LH mean pulse amplitudes are encountered in early, mid-, and late follicular and luteal phases. In general, pulsatile secretion is lower in amplitude but more frequent during the follicular phase compared with the luteal phase. On the other hand, alterations of the pulsatile LH secretion are found in virtually every menstrual disorder.

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**Table 1. Differences in low-threshold mechanosensitivity between pain conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Low-Threshold Mechanosensitivity</th>
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<tbody>
<tr>
<td>TMD mostly muscle-related</td>
<td></td>
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<tr>
<td>Hollins et al., 1996</td>
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<tr>
<td>Cervicobrachalgia</td>
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<td>Voerman et al., 2000</td>
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<tr>
<td>Experimental heat pain</td>
<td>Hypoesthesia</td>
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<td>Apkarian et al., 1994</td>
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<tr>
<td>Saline-induced muscle pain</td>
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<tr>
<td>Stohler et al., 2001</td>
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<tr>
<td>Capsaicin</td>
<td>Normesthesia</td>
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<td>Kauppila et al., 1999</td>
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<td>Davis et al., 1995</td>
<td></td>
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<tr>
<td>Simone &amp; Ochoa, 1991</td>
<td></td>
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<tr>
<td>After 3rd molar extraction</td>
<td>Hyperesthesia</td>
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<tr>
<td>Eliav &amp; Gracely, 1998</td>
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</tbody>
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In humans, voluntary mouth opening is reduced because motor units of jaw closers fire in greater numbers and at higher frequency during painful jaw opening than in the absence of pain. Pain effects on mandibular posture seem to explain the patient’s observation of “teeth not fitting together properly,” a perception that is no longer noticed following the resolution of pain. Contrary to common assumptions, electromyographic data do not support the idea of jaw muscle hyperactivity and spasms at rest (in the overwhelming case majority), and much of the changes in pain, captured by surface electromyography of the jaw musculature, reflect changes in facial expressions caused by pain. Taken together, the inability to contract muscles forcefully and rapidly seems to reduce the risk of further damage to the body, while the typical facial expressions and gestures of pain are indicators to others that the person is in pain, is suffering, and is in need of help and sympathy (Figure 4).
Hypopulsatility, the response pattern associated with persistent stress, suppresses both LH and follicle stimulating hormones (FSH), resulting in loss of normal cyclicity and menstrual irregularity. Under the condition of normal cyclicity, hypothalamic opioid activity is high during the luteal phase and low during menses. The underlying mechanisms are believed to be as follows. Hypothalamic neurons, containing b-endorphin, show maximal release when both estradiol and progesterone (luteal) are present. These neurons with their cell bodies are located in close proximity to neurons secreting GnRH. Because b-endorphin has been shown to decrease LH secretion, and naloxone reverses the effect, this hypothalamic neural substrate is implicated in the decline in LH pulse frequency during the luteal phase and provides a basis to rationalize the interaction of pain-stress and reproductive function.

Cause of Pain

The above points highlight effects of pain on other systems, suggesting the initiation of subsequent reactions that can explain much of the signs and symptoms, including many comorbid complaints associated with states of chronic orofacial pain. Understanding of these regulatory, mostly adaptive processes may suggest novel interventions to manage troublesome symptoms other than pain, for which the efficacy of current approaches leaves a lot to be desired. In this respect, I believe that symptom management with greater target specificity and efficacy than current approaches should become a realistic “next-level” treatment focus in support of the sizeable population of patients with chronic orofacial pain. At the same time, improved understanding of the pathogenesis of symptoms will lead to a better understanding of the response heterogeneity and possibly to the cause of pain itself.

Not many leads exist to suggest an underlying cause of chronic pain, and attempts to produce experimental states of lasting pain result in self-limiting pain states, requiring a repetitive or sustained pain-causing stimulus to maintain pain. There is one exception, however. The first clue pointing to the nerve growth factor (NGF) in long-lasting craniofacial pain came from a Phase I clinical safety trial in which subcutaneous and intravenous injections of recombinant human nerve growth factor (rhNGF) were given to healthy human volunteers. At doses ranging up to 1 mg/kg, NGF caused pain in the bulbar, jaw, and truncal musculature, which varied in duration and severity in a dose-dependent manner. Subjects compared the resulting pain with prior experiences of “overuse” muscle pain. Pain tended to worsen with chewing and was noticed with swallowing and eye movements.

Additional response features of rhNGF-induced pain depended on the mode of application. Subcutaneous application of rhNGF caused hyperalgesia at the injection site that lasted up to forty-nine days; generalized myalgia occurred sixty to ninety minutes after intravenous administration. Women tended to be more susceptible to NGF than men. This observation is consistent with the female excess, most notably in the childbearing ages, among sufferers of many pain conditions, pointing to the vulnerability of women to experience more frequent and more serious pains than men.
Summary

Individual variation in the neuroendocrine and autonomic pain-stress response and the consequences of pain on sensory, motor, immune and reproductive functions, and mood seem to account for the broad range of comorbid complaints linked to chronic orofacial pain. Susceptibility to a particular response appears to explain the intra-individual differences in disease expression. A breakthrough in understanding and management of these often devastating conditions depends on the broad engagement of the dental profession, acknowledging case attributes beyond simple clinical measures such as palpation scores, range of mandibular motion, and TMJ joint sounds.

REFERENCES


