CHRONIC OROFACIAL PAIN AND ENDODONTICS: DIAGNOSTIC AND THERAPEUTIC CHALLENGES

https://doi.org/10.56238/sevened2024.029-005

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ABSTRACT

Orofacial pain encompasses conditions of dental, musculoskeletal, and neuropathic origins, demanding accurate differential diagnosis to prevent mistreatment. Acute pain typically stems from pulpitis and periapical infections, whereas chronic pain arises from neuroplastic alterations and central sensitization. Neuropathic pain, such as trigeminal neuralgia, is characterized by its intensity and resistance to standard analgesics. Musculoskeletal pain, often linked to temporomandibular disorders, manifests diffusely, intensifying under emotional stress. Effective chronic orofacial pain management requires a multidisciplinary approach, combining pharmacological and non-pharmacological strategies, including physiotherapy and cognitive-behavioral therapy. Emerging interventions, such as ion channel modulators and transcranial stimulation, showcase advances in neuroscience, offering potential for improved outcomes. Recognizing phenotypic variations in orofacial pain is key to accurate diagnosis and optimal care.

Keywords: Orofacial Pain. Endodontics. Trigeminal neuralgia. Central Awareness. Multidisciplinary Therapy. Trilad Theory. Human reasoning.

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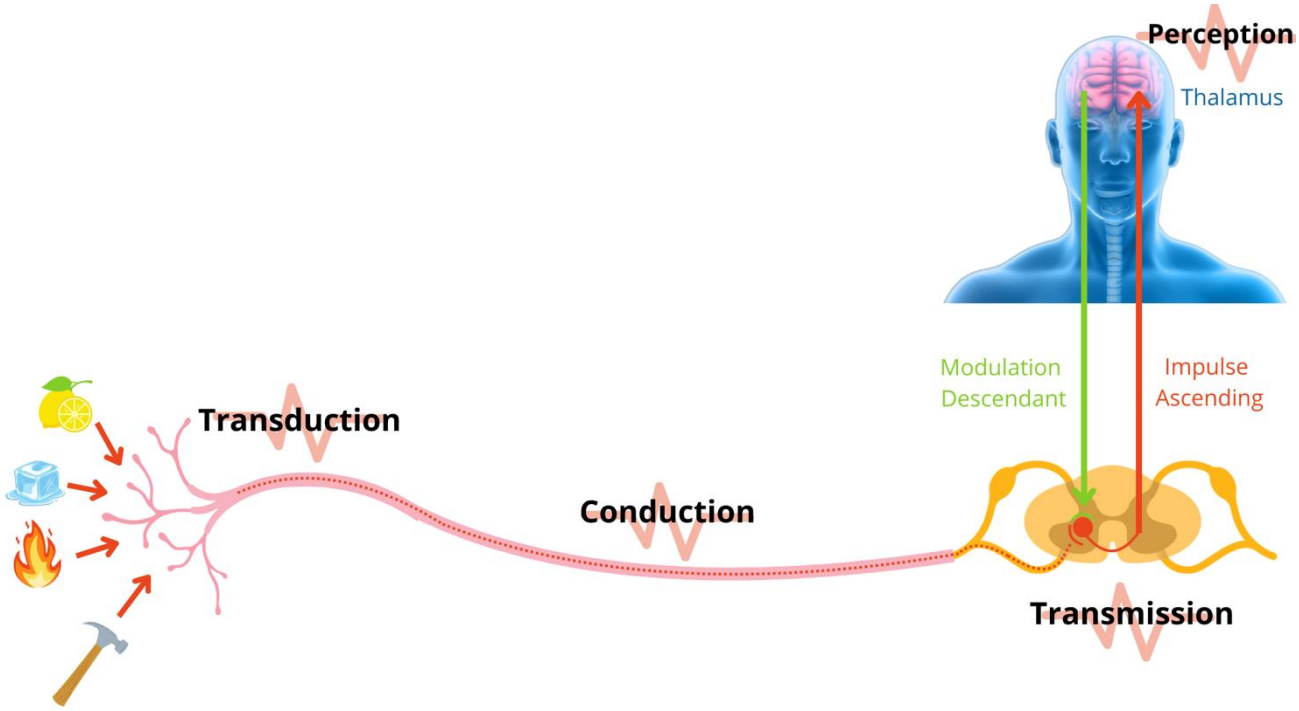
INTRODUCTION

With the increasing complexity of diagnosing and treating chronic orofacial pain, the application of the Trilad Theory offers healthcare professionals a new approach that goes beyond traditional therapeutic responses (SROUR 2022 and 2023). This theory allows that, instead of choosing between physical or psychological treatments in a binary way, multiple alternatives can be considered, promoting a broader management adapted to the needs of each patient (SROUR & MACHADO 2024; SROUR *et al.* 2024). This approach allows for a more holistic and individualized treatment, reflecting the sensory and emotional complexity of pain described by the International Association for the Study of Pain (IASP).

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. As the IASP clarifies, pain encompasses both physical and psychological dimensions, being a multifaceted experience influenced by sensory-discriminative, affective-motivational and cognitive-evaluative aspects. From an evolutionary perspective, pain plays a critical biological function, alerting the body to threats and promoting behaviors that protect against injury (RAJA, *et al.;* 2020).

At the cellular level, pain is initiated by nociceptors, specialized nerve endings that respond to harmful stimuli such as mechanical pressure, temperature extremes, or chemical signals. Nociceptors transduce these stimuli into electrical signals through the activation of ion channels, such as TRPV1 and sodium channels (NaV1.7). These signals are transmitted through peripheral nerves to the dorsal horn of the spinal cord, where they can undergo modulation before ascending to higher brain centers such as the thalamus and cortex. In chronic pain, these signaling pathways can become sensitized, resulting in hyperalgesia (increased sensitivity to painful stimuli) or allodynia (pain caused by normally non-painful stimuli) (ROTPENPIAN & YAKKAPHAN, 2021). Behaviorally, pain elicits a wide range of responses, from withdrawal and avoidance behaviors to psychological reactions such as anxiety and depression (TANNER, *et al.,* 2022).

Figure 1: Transmission scheme, through peripheral nociceptors, of pain caused by chemical, physical or mechanical stimuli.



Pain is much more than a symptom, it is a subjective experience and a major clinical challenge, as quantifying a qualitative report through traditional intensity scales does not capture the full complexity and depth of this phenomenon (SROUR & MACHADO, 2024). What is pain to you? What do you call pain? What was the worst painful experience you felt? It is possible to name pain the most diverse sensations such as tightness, discomfort, burning, itching, twisting, among an infinity of possibilities that the patient will simply name as "pain".

Pain is broadly categorized as acute or chronic, with duration being the determining factor for this classification. Acute pain is typically short-lived (less than three months) and serves as a protective mechanism in response to injury or inflammation. It is usually localized, and the clinician can easily attribute cause and effect, that is, the tissue injury that was able to activate nociceptors and cause this pain is visible and easily identified. In contrast, chronic pain persists beyond the normal healing period, often lasting more than three months, and may continue even after the original lesion has resolved. Chronic pain is more complex, often involving central sensitization and neuroplastic changes in the central nervous system (CNS), and it is not possible to identify the cause and the pain reported by the patient in such a simple way. The prolonged nature of chronic pain is often associated with psychological responses such as depression, anxiety, and stress, which further complicates its management (RAJA, *et al*.; 2020).

According to Srour *et al.* (2024), the Trilad Theory proposes a third response in addition to the traditional fight-or-flight mechanism, "freezing", which expands the possibilities of reaction in stressful situations, allowing a more integrative and adaptive approach to human behavior, which can be extrapolated to the analysis of orofacial pain.

Acute pain has a protective action and is directly related to an activation of peripheral nociceptors. It takes a painful stimulus, be it physical, chemical or mechanical, for the trigger to be triggered. Generally, with the healing of this affected tissue, the pain will also cease to exist. Chronic pain, on the other hand, is not protective in nature, that is, it is not necessarily linked to an identifiable tissue injury. It lasts longer than 3 months and is often associated with psychological factors such as irritability, sadness, social distancing, difficulty sleeping and daily activities. This pain occurs mainly through central pain mechanisms, and neuroplastic changes in the central nervous system (RAJA, *et al.;* 2020).

However, classifying pain in a binary way, as acute or chronic, may represent a simplistic view of the complex's mechanisms involved in the painful sensation. For Srour (2023), human thinking tends to follow this binary pattern, limiting decision options to extremes such as yes/no or positive/negative. The Trilad Theory (SROUR, 2022, 2023, and 2024), expands this reasoning by allowing the consideration of multiple alternatives, offering a more complex and flexible approach to problem solving, including for issues related to pain diagnosis.

There is no doubt that orofacial pain represents a complex and multifaceted challenge for health professionals, covering a wide range of conditions with diverse etiologies. These conditions can be broadly categorized into dental, musculoskeletal, neuropathic, and idiopathic origins. Understanding the full range of diagnoses and their associated phenotypes is crucial to providing effective treatment and avoiding misdiagnosis or overtreatment. The Trilad Theory offers a way to integrate the various dimensions involved in pain (SROUR, 2022), recognizing that orofacial pain is a multifaceted experience. According to this theory, we must overcome dualistic thinking, allowing a more comprehensive view of situations and offering multiple alternatives for decision-making, which can be applied in diagnosis and treatment planning in various areas, such as medicine and dentistry.

The application of the Trilad Theory, by promoting a broader approach to human reasoning (SROUR, 2023), is essential to avoid inadequate pain management, which can have not only physical, but also psychological and social consequences (WU *et al,* 2020). By recognizing the complexity of orofacial pain, we must seek a more accurate diagnosis and a more comprehensive treatment plan, reducing the risk of overtreatment and, consequently, the economic and social impacts that chronic pain imposes. Effectively addressing pain goes

beyond clinical concerns – it is a critical societal responsibility that encompasses medicine, dentistry, and the national health system (HONDA *et al.,* 2018).

Chronic orofacial pain, including dentoalveolar pain, presents substantial challenges for dental practice, especially due to its multifactorial nature and coexistence with other painful conditions. Chronic pain in this region can be particularly difficult to diagnose, as many of its symptoms overlap with those of other diseases, such as temporomandibular disorders (TMDs) and trigeminal neuropathic pain. Due to this overlap, many patients undergo inadequate treatments, such as endodontic treatments and tooth extractions, without their complaints being resolved (PIGG, *et al*., 2021).

Studies show that between 5% and 24% of patients report persistent pain after endodontic treatments. Odontogenic pain, by itself, is already one of the most prevalent in cases of orofacial pain, but it is often confused with pain of other origins, such as muscle or neuropathic pain, requiring a detailed and careful diagnostic evaluation (NIXDORF, *et al.,* 2015). In some cases, the pain may be related to TMD or other myofascial conditions, which requires the practitioner to accurately differentiate the source of the discomfort to avoid unnecessary procedures (WRIGHT; 2000). In addition, the increased sensitization of the trigeminal and facial nerves, observed in chronic orofacial pain, contributes to the complexity of the diagnosis.

Chronic orofacial pain is a condition that, if poorly managed, can result in treatments that not only fail to resolve the pain but can also exacerbate the condition. This phenomenon of "therapeutic failure" points to the importance of understanding not only odontogenic pain, but also neuropathic and muscular pain that can mimic or coexist with it (SCHOLZ & WOOLF, 2007). This chapter explores in detail the challenges of diagnosing and treating chronic orofacial pain, with an emphasis on the difficulties faced by endodontics professionals when trying to differentiate odontogenic pain from other forms of orofacial pain. Pathophysiological mechanisms, etiological factors, and comorbidities associated with pain will be discussed, as well as the multidisciplinary therapeutic approaches recommended for its effective management.

Pain Quality Descriptors	
Acute Pain	**Chronic Pain**
1. **Stabbing** (severe, sharp pain, like a stab) 2. **Throbbing** (pulsating, often associated with inflammation) 3. **Burning** (burning sensation, common in burns) 4. **Cutting** (as if being cut) 5. **Pungent** (a piercing, sharp pain) 6. **Piercing** (as if something is piercing the skin) 7. **Sharp** (clear and distinct pain) 8. **Spasmodic** (intermittent pain that suddenly arises)	1. **Deaf** (constant and not very intense, but persistent pain) 2. **Diffuse** (scattered pain, difficult to locate) 3. **Dull** (persistent and dull pain, but not sharp) 4. **Deep** (pain that appears to be localized to internal tissues or organs) 5. **Burning** (continuous burning sensation, common in chronic neuropathies) 6. **Heavy** (feeling of heaviness or constant pressure) 7. **Persistent** (pain that does not cease over time) 8. **Pulsatile** (appears to pulsate rhythmically, but continuously over time)

TYPICAL PHENOTYPES OF OROFACIAL PAIN AND PATHOPHYSIOLOGY

Facial pain conditions manifest through different phenotypes, each influenced by distinct underlying pathophysiological mechanisms (TANNER *et al.,* 2022). These conditions can be classified according to their nociceptive, neuropathic, musculoskeletal, vascular, or idiopathic origins, which helps in the definition of appropriate diagnostic and treatment strategies (ROMERO-REYES *et al*., 2023).

Odontogenic pain arises due to damage to dental tissues, mainly involving inflammation or infection, such as in dental caries, pulpitis or periapical abscesses (MACAULEY, O'DONNELL & DUNCAN, 2013). These conditions are considered nociceptive, as they activate normal pain pathways in response to tissue damage. Patients with odontogenic pain often describe it as intense and localized, and the symptoms are aggravated by external stimuli, such as cold or heat (BENKO, 2012; SPLIETH & TACHOU, 2013). The pain can be quite acute, reflecting the acute inflammatory nature of dental tissues (ROMERO-REYES, *et al*., 2023).

Neuropathic pain, on the other hand, is associated with nerve damage or dysfunction, as seen in conditions such as trigeminal neuralgia, postherpetic neuralgia, and glossopharyngeal neuralgia. These conditions result from injuries or diseases that affect the nerves responsible for transmitting pain signals. Trigeminal neuralgia, for example, is characterized by sudden episodes of severe, stabbing pain, often triggered by stimuli that would not normally cause pain, such as light touch, chewing, or speech (SPENCER & GREMILLION, 2007; TANNER *et al.,* 2022). The pain is usually described as similar to an electric shock, reflecting the anomalous activation of nerve fibers (TANNER *et al.,* 2022). Neuropathic pain is notoriously difficult to treat with conventional painkillers, often requiring medications that act specifically on nerve pain, such as anticonvulsants or antidepressants (SPENCER & GREMILLION 2007).

Musculoskeletal pain in the orofacial region usually originates from conditions such as temporomandibular disorders (TMD) or bruxism, which involve the muscles and joints of the jaw. This type of pain is described as dull and diffuse, often radiating to adjacent areas such as the temples or ears (LABANCA *et al*., 2023). TMD, for example, may present with additional symptoms, such as jaw stiffness or popping, especially during movements such as chewing or talking. Bruxism, which involves grinding or clenching of the teeth, can exacerbate this pain, particularly in patients under stress (FERRILLO *et al*., 2022). In these situations, pain is more associated with the musculoskeletal system than nerve injury, and treatments often focus on reducing muscle tension or correcting joint dysfunctions (BUSSE *et al.,* 2023).

Vascular pain, as occurs in migraines or cluster headaches, is characterized by throbbing or pulsating sensations, often accompanied by autonomic symptoms such as tearing or nasal congestion (CHOI, LEE & PARK, 2023). Cluster headaches, for example, are marked by excruciating pain located around one eye, often described as burns or stab wounds. The episodic nature of these headaches, along with their association with vascular changes, points to a dysregulation of blood flow in the cranial vessels (KAWAGUCHI & ICHINOHE, 2024). These pains are often triggered by environmental factors or stress, and treatment may include medications that target vascular tone, such as triptans, or preventive therapies, such as calcium channel blockers (JALALI *et al.,* 2014).

Idiopathic pain, including persistent idiopathic facial pain (PID) and atypical odontalgia (OA), is poorly understood in origin and has no clear physical cause. These conditions are thought to be related to central sensitization mechanisms or nociplastic pain, in which the central nervous system becomes hypersensitive to painful stimuli (LABANCA *et al*., 2023; MAY et al., 2023). Patients with idiopathic pain often experience chronic pain, which is imprecisely located and difficult to describe, which can lead to frustration and lead to misdiagnosis (SPENCER & GREMILLION, 2007). In the case of PIDD, pain can be constant, without any clear association with identifiable triggers or injuries, making its management challenging. Treatments often focus on addressing the central sensitization component, utilizing medications such as antidepressants or anticonvulsants (GERWIN, 2020).

In summary, each facial pain condition has distinct phenotypic characteristics and requires specific diagnostic and therapeutic approaches. Understanding the underlying pathophysiology is essential for effective treatment, as management strategies vary significantly across nociceptive, neuropathic, musculoskeletal, vascular, and idiopathic pain conditions (TANNER *et al.,* 2022; ROMERO-REYES *et al.,* 2023).

Type of Pain	Definition	Key features
Neuropathic	Neuropathic pain occurs due to injury or dysfunction in the nervous system, whether peripheral or central, resulting in an anomalous transmission of pain signals.	**Sensation of electric shock:** Neuropathic pain is often described as a sharp, intense pain, similar to electric shocks, burns, or twinges. **Allodynia:** The presence of pain resulting from normally non-painful stimuli, such as a light touch to the skin, is common in patients with neuropathic pain.
Nociceptive	Nociceptive pain results from the activation of nociceptors, which are receptors specialized in detecting actual or potential tissue lesions. It is the most common form of pain associated with inflammation or physical damage.	**Precise location:** Nociceptive pain is usually well localized and is directly related to the injured area, as occurs in burns, trauma, or inflammation. **Response to common painkillers:** This type of pain responds well to treatment with traditional painkillers, such as anti-inflammatories and opioids, which work to control inflammation and pain.
Nociplastic	Nociplastic pain occurs in the absence of tissue injury or overt nerve damage. It is related to central sensitization, in which the central nervous system amplifies pain signals, even in the absence of a clear nociceptive or neuropathic source.	**Generalized tenderness:** Patients with nociplastic pain, such as in fibromyalgia, may report pain that is diffuse, difficult to locate, and disproportionate to the injury or external stimulus. **Resistance to conventional analgesics:** Nociplastic pain does not respond well to traditional analgesic and anti-inflammatory treatments, requiring therapeutic strategies that involve central nervous system modulators, such as antidepressants and anticonvulsants.

THE CHALLENGE OF DIFFERENTIAL DIAGNOSIS

The differential diagnosis between odontogenic pain and non-odontogenic pain is a complex task that requires a deep understanding of the clinical characteristics of each type of pain. Odontogenic pain, commonly related to pulp and periapical inflammation, is one of the most frequent complaints in endodontic practice. However, other forms of pain, such as those of muscular and neuropathic origin, can simulate odontogenic pain, complicating the diagnosis (PIGG, *et al.,* 2021).

ENDODONTIC PAIN

Dental pulp is a specialized connective tissue that is found in the central portion of the teeth. This tissue is highly innervated and vascularized, being responsible for maintaining the

vitality of the tooth (RONAN *et al.*, 2024). The pulp is composed of four main zones: the odontoblastic layer, the cell-free zone (Weil's layer), the cell-rich zone, and the pulp nucleus (BENDER, 2000).

Odontoblasts, located at the interface between the pulp and dentin, are specialized cells that produce dentin, a mineralized tissue that protects the pulp. In addition, these cells play an important role in the transmission of painful stimuli, as their prolongations extend to the dentin tubules, allowing the conduction of nociceptive signals (RONAN *et al.*, 2024).

The innervation of the pulp is mostly sensory, composed of nerve fibers from the trigeminal ganglion, responsible for the perception of painful stimuli. Nerve fibers are divided into two main types: A-delta fibers and C fibers. A-delta fibers, which are myelinated, quickly transmit the sensation of acute and localized pain, while C fibers, which are unmyelinated, lead to slower and more diffuse pain, often associated with inflammatory processes (BENDER, 2000; RONAN *et al.,* 2024).

The mechanisms of pain of pulp origin are complex and involve both mechanical and thermal and chemical stimuli. The hydrodynamic effect, which results from the movement of fluid within the dentin tubules, is one of the main mechanisms responsible for dental pain. When there is a rapid variation in temperature, such as the application of cold or heat, the fluid in the tubules moves, deforming the nerve endings and triggering a painful response. This movement is mainly detected by A-delta fibers, which are responsible for the sensation of sharp and short pain (BENDER, 2000; ABD-ELMEGUID & YU, 2009).

Another important factor in pulp pain is inflammation, especially in cases of pulpitis, which can be reversible or irreversible. In reversible pulpitis, the inflammation is mild and usually results from stimuli such as superficial cavities. Irreversible pulpitis, on the other hand, occurs when the inflammation is intense and extensive, leading to pulp necrosis. In these cases, the C fibers are the main ones involved, transmitting a dull, persistent and frequently referred pain (BENDER, 2000; ABD-ELMEGUID & YU, 2009).

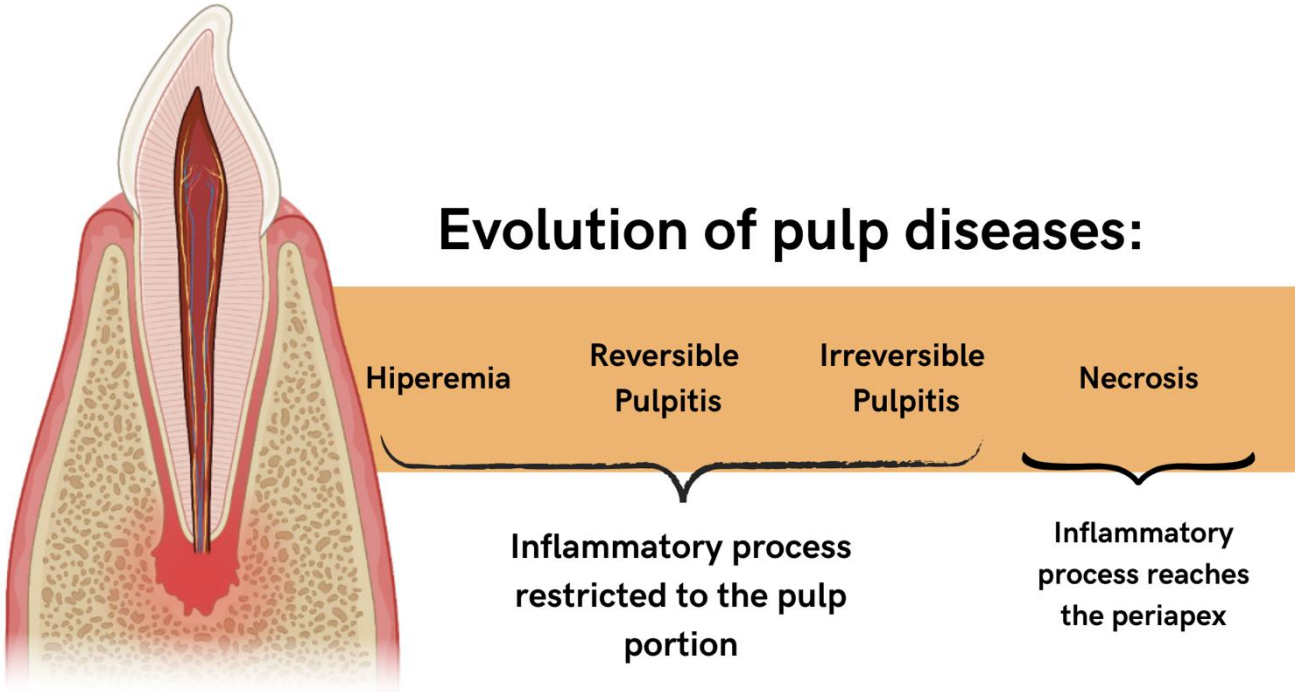
During the inflammatory process, the release of inflammatory mediators, such as substance P and calcitonin gene-related peptide (CGRP), sensitizes nerve endings, lowering the threshold for the generation of action potentials. In addition, inflammation increases vascular permeability, leading to increased intrapulp pressure, which further intensifies the sensation of pain (ABD ELMEGUID & YU, 2009; RONAN *et al.,* 2024). In chronic conditions, the pulp may undergo neuroplastic changes, resulting in hyperalgesia (increased sensitivity to painful stimuli) or allodynia (pain caused by normally non-painful stimuli). These changes are often observed in patients with chronic pulpitis or pulp necrosis, in whom pain may persist even after removal of the initial stimulus (BENDER, 2000; RONAN *et al.,* 2024).

Apical periodontitis is an inflammatory condition that arises as a result of pulp necrosis, usually caused by bacterial infections that penetrate the dental pulp through deep cavities, fractures, or trauma. Pulp death creates an environment conducive to the proliferation of anaerobic microorganisms that invade the root canals and establish themselves in the periapical region (LILIS *et al.,* 2024).

As bacteria and their byproducts, such as toxins and endotoxins, spread through the necrotic root canals, they reach the periodontal ligament and alveolar bone around the root apex, triggering an acute inflammatory response. The immune system reacts to the bacterial influx by releasing inflammatory cells, such as neutrophils, macrophages, and lymphocytes, which accumulate in the periapical area and attempt to fight infection (WOLF *et al*., 2019). This periapical inflammation is characterized by the activation of osteoclasts, cells responsible for bone resorption, which leads to the destruction of the alveolar bone around the apex of the root. This process of periapical bone loss is mediated by several inflammatory cytokines, including IL-1, TNF-α, and RANKL, which stimulate osteoclastogenesis. The release of inflammatory mediators not only causes bone destruction but also sensitizes nerve fibers in the region (LILIS, *et al.,* 2024).

In the context of pain, nociceptors, which are nerve endings specialized in detecting painful stimuli, are activated by the products of inflammation and increased pressure in the periapical space caused by edema and the exudation of inflammatory fluids. The activation of these nociceptors results in the transmission of painful signals to the central nervous system, creating a sensation of intense and localized pain, which is characteristic of apical periodontitis. This pain is usually exacerbated by mechanical stimuli, such as chewing or percussion, due to pressure on the inflamed tissue around the apex of the tooth. Thus, understanding pulp neurophysiology and the mechanisms involved in pulp pain is critical for the proper diagnosis and treatment of pulp pathologies, allowing dental professionals to effectively manage painful conditions that affect patients.

Figure 2: Evolution of pulp disease. In all phases, the patient may present pain, in different ways and qualities.



Diagnosis	Quality of pain	Peripheral Mechanism	Central Mechanism	Clinical Signs
Pulpitis	Sharp stabbing, throbbing	Inflammation of the dental pulp leading to sensitization of nociceptors	Peripheral sensitization can lead to prolonged signs of pain.	Severe and prolonged pain, especially at night, sensitivity to heat and cold, and may progress to spontaneous pain without any stimulus.
Periapical Abcess	Acute stabbing, localized	Inflammatory response to infections causing pressure on periapical tissues	Central sensitization possible in cases of prolonged infection.	Swelling, redness, pus drainage, tooth sensitivity to pressure, and possible systemic signs such as fever.
Pain after endodontic treatment	Acute to chronic, with varying pain intensity	Post-treatment trauma or infection affecting surrounding tissues	Central sensitization in chronic cases.	Pain following endodontic treatment, swelling, and tenderness that may persist or recur.
Trinca Radicular	Acute stabbing type	Microfractures cause stimulation of the nociceptors of the dental pulp.	Central sensitization in chronic cases.	Sharp pain when biting or chewing, sensitivity to cold, and discomfort that may come and go.
Dentin Hypersensitivity	Acute short-term stabbing type	Exposure of dentin tubules leading to fluid	It is not typically involved.	Sensitivity to hot, cold, or sweet stimuli, with no

		movement that stimulates nociceptors		visible signs of tooth decay.

MYOFASCIAL PAIN AND TEMPOROMANDIBULAR DISORDERS (TMD)

The temporomandibular joint (TMJ) is one of the most complex joints in the human body, being responsible for the opening, closing, and sliding movements of the jaw. It is composed of bone, ligament and muscle structures that allow a wide range of movements necessary for functions such as chewing, speaking and swallowing. Anatomically, the TMJ involves the head of the mandible (mandibular condyle), the glenoid cavity of the temporal bone, and the articular disc, a fibrocartilaginous structure that acts as a shock absorber, preventing direct contact between bones during movement (SESSLE, 2014; TANNER *et al.,* 2022).

Temporomandibular disorder (TMD) is a condition that affects the TMJ and masticatory muscles, and is one of the main causes of orofacial pain. Pain in TMD can be divided into three main categories: muscular, joint, and mixed, depending on the structures involved.

Muscle Pain

Muscle pain in TMD is usually related to dysfunctions in the muscles of mastication, such as the masseter, temporalis, and pterygoid. Conditions such as bruxism, characterized by clenching or grinding of the teeth, can lead to muscle fatigue and pain. This type of pain is usually described as dull and diffuse, radiating to adjacent areas such as the temples and ears. Pain can be exacerbated by jaw movements or even at rest, depending on the severity of muscle inflammation (FERRILLO *et al.,* 2022).

In addition, emotional stress has often been associated with muscle pain in TMD, since patients with high levels of anxiety or depression tend to have greater tension in the masticatory muscles. The pathophysiology involves both activation of muscle nociceptors and central sensitization, resulting in hyperalgesia (FERRILLO *et al.,* 2022; ROMERO-REYES *et al.,* 2023).

Joint Pain

Joint pain in TMD is related to alterations within the temporomandibular joint itself. The main cause of joint pain is joint disc displacement, a condition in which the disc moves from its normal position, causing friction between the mandibular condyle and the glenoid cavity. This displacement can result in sharp pain, often associated with joint noises, such as clicking

or crackling during the opening and closing of the jaw (SESSLE, 2014; ROMERO-REYES *et al.,* 2023).

In more advanced cases, joint degeneration can occur, leading to osteoarthritis, a degenerative condition that affects the underlying cartilage and bones. Joint pain is typically described as deep, localized pain, with worsening during jaw movement or pressure on the joint (TANNER *et al.,* 2022). Joint inflammation can also lead to increased sensitivity and restriction of jaw movements.

Mixed Pain

Mixed pain in TMD involves both muscle and joint components and is the most common type of temporomandibular pain. Patients with mixed pain often report a combination of symptoms, such as diffuse, dull pain in the masticatory muscles, associated with joint clicking and restriction of movement. Mechanical overload on the jaw muscles and joints can lead to chronic inflammation, further exacerbating pain (TANNER *et al.,* 2022). This combination of muscle and joint factors makes the management of mixed pain more challenging, requires a multidisciplinary approach to treatment, which may include physical therapy, stress management, and the use of occlusal devices (FERRILLO *et al.,* 2022; ROMERO-REYES *et al.,* 2023).

Understanding the mechanisms of pain in TMD, differentiating its muscular, joint, and mixed causes, is crucial for effective diagnosis and treatment. Targeted treatments that address both inflammatory components and biomechanical and psychological factors are essential for the proper management of this complex condition.

Diagnosis	Quality of pain	Peripheral Mechanism	Central Mechanism	Clinical Signs
Temporomandibular Disorder (TMD)	Chronic, massive and profound	Muscle or joint dysfunction, inflammation	Central sensitization, possibly leading to chronic pain syndromes	Jaw pain, limited range of motion, clicking or popping sounds, headaches, and muscle tenderness.
Referred pain	Opaque, diffuse, variable intensity	It originates from other structures such as the ear, muscles or sinuses and is referred to the teeth	Central processing of referred pain may involve sensitization	Non-localized pain in one tooth, no apparent dental pathology, possible pain in nearby structures.

NEUROPATHIC PAIN

Neuropathic pain, defined by the International Association for the Study of Pain (IASP) as that resulting from injury or dysfunction of the somatosensory nervous system, is another condition that can mimic odontogenic pain. In the orofacial setting, neuropathic pain can be caused by lesions in the trigeminal, facial, or peripheral nerves that innervate the oral cavity and adjacent structures. Trigeminal neuralgia is a classic example of neuropathic pain that can be confused with odontogenic pain due to its location and the paroxysmal nature of the painful episodes (SPENCER*, et al.,* 2007)

Studies indicate that about 3% to 5% of patients with persistent orofacial pain have neuropathic pain, and many of them have undergone invasive dental treatments without the actual cause of the pain being treated. Orofacial neuropathic pain is often accompanied by abnormal sensations such as allodynia (pain caused by stimuli that are not normally painful) and hyperalgesia (increased sensitivity to painful stimuli) (SCHOLZ, *et al.,* 2007).

The differentiation between orofacial pain and headache is related to the trigeminal nerve dermatomes that are involved. Headache affects the ophthalmic branch (V1) of the trigeminal nerve, as well as the dermatomes of the greater and lesser occipital nerves. On the other hand, facial pain, according to the most recent International Classification of Headache Disorders (ICHD-3), is defined as pain located below the infraorbitomeatal line, in front of the pinna and above the neck – a region innervated by the maxillary (V2) and mandibular (V3) branches of the trigeminal nerve. Unlike headaches, which are usually primary, facial pain is more often attributed to secondary causes. Inflammatory or infectious processes in craniofacial structures, such as sinusitis and dentoalveolar diseases, are common causes of facial pain (GAUL, *et al*., 2007; GAUL, *et al.,* 2008; ZIEGELER, *et al*., 2019). In some cases, diagnostic tests do not identify organic lesions, and facial pain is considered the disease itself – in these cases, the patient is diagnosed with idiopathic (primary) orofacial pain (MAARBJERG, *et al.,* 2017).

Diagnosis	Quality of pain	Peripheral Mechanism	Central Mechanism	Clinical Signs
Neuralgia Trigeminal	Chronic, similar to electric shock	Compression or irritation of the trigeminal nerve	Central sensitization leading to hypersensitivity	Sudden, severe facial pain triggered by touching, chewing, or speaking, usually on one side of the face.
Atypical facial pain/ Idiopathic persistent facial pain	Chronic, deep, constant	No identifiable peripheral cause	Central sensitization leading to	Diffuse, poorly localized facial pain with no

			persistent and unexplained pain	obvious dental or sinus problems.
Postherpetic Neuralgia	Chronic, burning, stabbing-like	Peripheral nerve damage after herpes zoster infection	Central sensitization involving abnormal CNS pain processing	Persistent pain after the rash has healed, usually associated with skin tenderness and burning sensations.
Glossopharyngeal neuralgia	Severe, like an electric shock, radiating	Glossopharyngeal nerve compression or irritation	Central sensitization due to prolonged nerve irritation	Sudden pain in the throat, ear, or base of the tongue, triggered when swallowing or speaking.
Neuropatia Periférica	Chronic, burning, tingling	Peripheral nerve damage	Central sensitization in cases of chronic nerve injury	Numbness, tingling, or burning pain in the affected area, usually in glove or sock distribution.
Cluster Headache	Serious, stabbing, unilateral	Neurovascular inflammation affecting the autonomic pathways of the trigeminal	Central mechanisms include hypothalamic involvement	Severe pain around one eye, tearing, nasal congestion, and restlessness during an attack.
Migraine	Throbbing, pulsatile, unilateral	Neurovascular dysfunction involving the trigeminal system	Central sensitization and cortical spreading depression	Moderate to severe throbbing headache, nausea, photophobia, and aura in some cases.
Giant Cell Arteritis	Muffled, throbbing, grave	Inflammation of the arteries, particularly the temporal artery	Central sensitization can occur if left untreated	Scalp tenderness, jaw lameness, vision problems, and systemic symptoms like fever or weight loss.
Bell's palsy	No pain or mild pain in some cases	Inflammation or compression of the facial nerve	Not normally involved	Sudden weakness or paralysis on one side of the face, drooping mouth or eyelid, and difficulty closing the eyes.

OTHER FACIAL PAIN

Associated with dental problems

Diagnosis	Quality of pain	Peripheral Mechanism	Central Mechanism	Clinical Signs
Dental Cavities	Sharp twinge type	Activation of nociceptors in response to bacterial invasion and decomposition	Not normally involved	Visible cavities, tooth sensitivity to sweets, hot or cold stimuli, and dark spots on the tooth surface.
Gingivitis	On the left, dolorido.	Inflammation of the gum tissues due to plaque buildup	Not normally involved	Red, swollen gums that may bleed while brushing or flossing, but no bone or insertion loss.
Periodontitis	Surda, persistent, painful	Inflammation and destruction of periodontal ligaments	Central sensitization in chronic cases	Gum recession, deep pockets, loose teeth, bleeding gums, and bad breath.
Periodontal Abcess	Acute, localized, throbbing	Infection leading to abscess formation and pressure on periodontal tissues	Not normally involved	Sore and swollen gums, pus discharge, tooth mobility and localized swelling.
Tooth fracture/ dislocation/avulsion	Sharp, Amateur, Intermittent	Trauma to the tooth causing direct stimulation of the nociceptors	Not normally involved	Visible dental involvement, sharp pain when chewing or biting, and sensitivity to temperature changes.
Root cyst	Surda, persistent	The formation of cysts causes pressure and inflammation in the surrounding tissues	Not normally involved	Painless swelling from slow growth, tooth displacement, or tooth mobility, often visible on x-rays.
Dry socket	High-pitched, twinge-like, throbbing	Loss of blood clot and bone exposure leading to activation of nociceptors	Not normally involved	Severe pain 2 to 3 days after tooth extraction, exposed bone in the socket, bad taste, and bad breath.
Impacted Tooth	Deaf, throbbing, localized	Pressure and inflammation in surrounding tissues due to impaction	Not normally involved	Swollen and tender gums, difficulty opening the mouth, and recurrent infections (pericoronitis).

Burning Mouth Syndrome	Chronic burning-type	Peripheral nerve damage or dysfunction	Central sensitization possibly involving changes in pain pathways	Persistent burning sensation on the tongue or other oral tissues, often with no visible abnormalities.
Sialodenitis	Deaf, painful, associated with swelling	Inflammation of the salivary glands causing activation of the nociceptor	Not normally involved	Swelling of the affected salivary gland, pain, dry mouth, and possibly fever.
Parotitis	Deaf, sore, localized	Inflammation or infection of the parotid gland	Not normally involved	Pain and swelling in the cheek region near the parotid gland, fever, and pus discharge in bacterial cases.
Osteomyelitis	Severe, latejante, persistent	Infection of the bone causing inflammation and necrosis	Usually not involved unless it becomes chronic	Swelling, pain, pus discharge, fever, and sometimes bone exposure.
Eagle Syndrome	Sharp, penetrating, radiating down the throat	Elongation of the styloid process by irritating the surrounding tissues	Not normally involved	Pain when turning the head, swallowing, or speaking, often radiating to the ear or throat.

Associated with infections of the sinuses and respiratory areas

Diagnosis	Quality of pain	Peripheral Mechanism	Central Mechanism	Clinical Signs
Sinusitis	Dude, pressure-like, often associated with nasal congestion	Inflammation of the sinus mucosa	Pain can be reported, but the central mechanisms are not primarily involved	Facial pressure, congestion, postnasal drip, and tenderness in the maxillary sinus area.
Nasal Polyp	Lightweight, pressure-like	Polyps causing obstruction and inflammation of the nasal tissues	Not normally involved	Nasal congestion, reduced sense of smell, and recurrent sinus infections.
Sinusite Maxilar	Deaf, pressure-like, often associated with nasal symptoms	Inflammation of the maxillary sinus mucosa	Pain can be reported, but the central mechanisms are not primarily involved	Facial pain, pressure and swelling, often with nasal and postnasal congestion.

Associated with cardio-vascular problems

Diagnosis	Quality of pain	Peripheral Mechanism	Central Mechanism	Clinical Signs
Carotidinia	Throbbing, high-pitched, localized	Inflammation of the carotid artery or surrounding tissues	Not normally involved	Carotid artery tenderness and pain, often associated with swelling or a palpable mass.

COMORBIDITIES AND RISK FACTORS

Patients with chronic orofacial pain often have comorbidities that further complicate diagnosis and treatment. Patients with TMD are almost three times more likely to develop migraines, in addition to being associated with other chronic pain conditions (AARON, BURKE & BUCHWALD, 2000; YAKKAPHAN, *et al.,* 2024), such as fibromyalgia, chronic fatigue syndrome, arthritis (MESIC, *et al.,* 2023), irritable bowel syndrome (COSTA, *et al.,* 2017; SLADE *et al.,* 2020) and chronic back pain. In addition, TMD can also be related to non-painful diseases, such as obstructive sleep apnea (MACHADO, *et al.,* 2024).

In addition to physical conditions, studies have revealed a strong relationship between chronic facial pain and psychological factors (MELEK, DEVINE, & RENTON, 2018). These factors significantly influence TMD, with up to 75% of TMD patients having psychological issues. These patients are more likely to develop anxiety, somatization, and depression, and emotional stress has a considerable impact on the condition (SÓJKA *et al.,* 2019). There is a significant correlation between stress and a higher rate of chronic TMDs. This reinforces the need for a multidisciplinary approach, involving not only dental professionals, but also physicians, psychologists, and physiotherapists (STANISZEWSKI *et al.,* 2018).

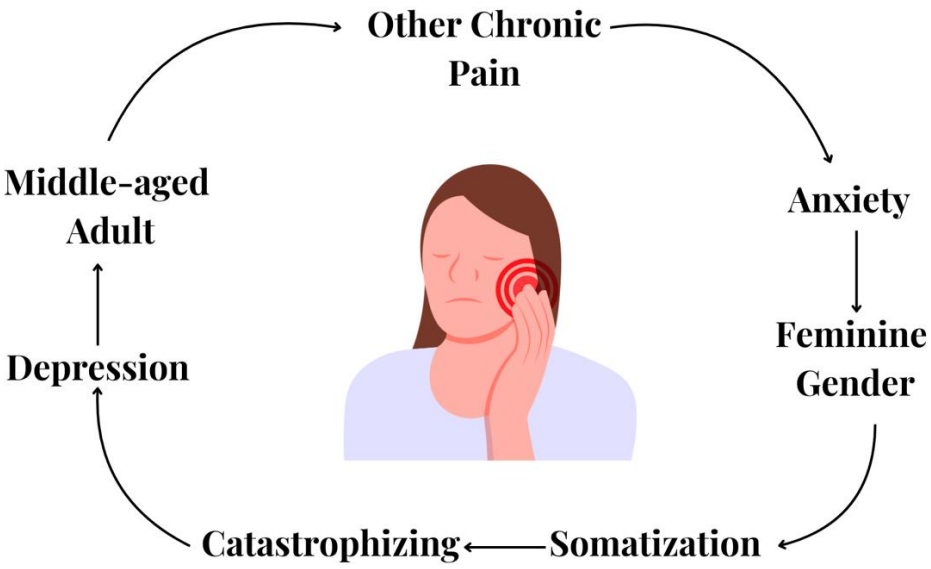
Data also indicate that TMD is more prevalent, long-lasting, intense, and frequent in women (KHAN, LIU, & TAO, 2024). Hormonal factors (PATIL, *et al.,* 2015; JEDYNAK, *et al.,* 2021), craniofacial anatomy (ALARCÓN, BASTIR & ROSAS, 2015; SHE, *et al.,* 2021), TRP channel engagement (WU, *et al.,* 2015; GONZÁLEZ-RAMÍREZ *et al.,* 2017; WANG, *et al.,* 2023), the opioid system (LIU, *et al.,* 2021), and the endocannabinoid system (NIU, *et al.,* 2012; WEERATHATAPHAN *et al.,* 2021), as well as psychosocial aspects (MEINTS &

EDWARDS, 2018; DEMIRCIOĞLU, ÖZKAL & DAĞ, 2022), have been suggested as possible contributors to this gender disparity (SORGE & TOTSCH, 2017).

In endodontics, studies have shown that women have a higher prevalence of apical periodontitis compared to men (BERLINCK *et al.,* 2015). In addition, women report greater pain intensity, higher consumption of analgesics, and less pain relief with the use of these medications compared to men (POLYCARPOU *et al.,* 2005; ESTRELA *et al.,* 2011; Nusstein and Beck, 2003). In a recent animal study, Lilis *et al.,* 2024 demonstrated that female mice exhibit unique gene expression patterns during apical infections compared to males, with nociceptors regulating the expression of these genes. The predominance of women in the study highlights the need for gender-specific diagnostic and treatment approaches, especially to understand how endodontic treatments can interfere with the emergence or exacerbation of TMD-related pain in women (CASALE, *et al.,* 2021).

The average age reported by patients with TMD is 40 years (MAIXNER, *et al.,* 2016; FERREIRA, SILVA & FELÍCIO, 2016; VALESAN, *et al.,* 2021). This age group is more susceptible to dental problems and temporomandibular joint (TMJ) dysfunctions due to cumulative wear and tear (BUSBY, *et al.,* 2014), suggesting the need for integrated dental and TMD management strategies.

Figure 3: Risk factors associated with chronic orofacial pain.



THERAPEUTIC APPROACHES

The treatment of chronic orofacial pain should be personalized and multidisciplinary, considering the peripheral, central, and psychological factors that contribute to the

perpetuation of pain (BENICZKY *et al*., 2005). Next, we discuss the main therapeutic approaches for chronic orofacial pain.

PHARMACOLOGICAL THERAPIES

Pharmacologic therapies for chronic orofacial pain include the use of anticonvulsants, such as gabapentin and pregabalin, which have been effective in treating neuropathic pain, and tricyclic antidepressants, such as amitriptyline, which are also used to reduce central sensitization. Nonsteroidal anti-inflammatory drugs (NSAIDs) and common pain relievers may be helpful in early stages of pain, but they are often insufficient to control long-term chronic pain (KIM, *et al*., 2021).

NON-PHARMACOLOGICAL THERAPIES

Non-pharmacological therapies, such as physical therapy, acupuncture, and cognitive-behavioral therapy, have been shown to be effective in the management of chronic orofacial pain. These approaches aim not only to reduce pain but also to improve the functionality and quality of life of patients by addressing the biopsychosocial aspects of pain.

Recently, interventions such as transcranial magnetic stimulation (TMS) and transcutaneous electrical stimulation (TENS) have been explored as therapeutic options for orofacial neuropathic pain, with promising results in some studies (KIM, *et al*., 2021).

The application of the Trilad Theory in dental practice allows the practitioner to explore a combination of disciplines in addition to traditional options (Srour 2022, 2023, 2024, Srour & Machado 2024, Srour *et al.* 2024). For example, when dealing with chronic orofacial pain, the dentist can integrate psychological approaches, muscle therapies, treatments that aim at the patient's emotional control, such as relaxation or mindfulness techniques, all within the same treatment plan.

EMERGING APPROACHES

Advances in neuroscience have opened new possibilities for the treatment of chronic orofacial pain. Among the emerging approaches are the use of ion channel modulators, gene therapies, and the use of stem cells to regenerate damaged nerve tissues. These therapies may provide new options for patients who do not respond to conventional approaches.

In addition, a better understanding of the genetic and epigenetic factors that influence orofacial pain may allow for the development of more personalized treatments, adjusted to the individual needs of each patient (KIM, *et al*., 2021).

FINAL CONSIDERATIONS

Chronic orofacial pain represents a major challenge for healthcare professionals, especially in endodontics, where confusion between odontogenic pain and other forms of pain can lead to unnecessary and ineffective treatments. Careful differential diagnosis, coupled with a deep understanding of the mechanisms underlying pain and associated comorbidities, is essential to ensure that patients receive the most appropriate treatment.

With the advancement of neuroscience research and the development of new therapeutic approaches, there is hope that professionals can, soon, offer more effective solutions for patients with chronic orofacial pain, significantly improving their quality of life.

Finally, the Trilad Theory and human reasoning does not see the neural system as an isolated structure, or a single way of stimulating and perceiving pain, and faces these mechanisms in a comprehensive way, where other aspects must be considered. Considering that this powerful system works together and not in isolation.

ACKNOWLEDGMENTS

This book chapter was developed with the support of research funding, provided in part by the Coordination for the Improvement of Higher Education Personnel – Brazil (CAPES) – Funding Code 001; by the National Council for Scientific and Technological Development – CNPq (INCT Oral Health and Dentistry) 406840/2022-9; 406261/2023-7; and by the Research Support Foundation of the State of Minas Gerais – FAPEMIG, grant numbers APQ-02105-18 and APQ-00927-23.

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