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From Nociception to Chronicity: Neurobiological Mechanisms of Orofacial Pain

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Abstract

The term orofacial pain encompasses a diverse group of disorders affecting the highly innervated oral, facial, jaw and associated tissues and constitutes one of the most frequent and disabling dental and medical complaints. It also has a different neurobiological basis from that of pain in other parts of the body due to its unique anatomical and functional organisation of the trigeminal system. The present review aims to map out the continuum of acute nociception to persistent chronic pain. It starts with peripheral transduction of the noxious stimulation by trigeminal nociceptors and the machineries that transduce the noxious stimulation into electrical signals, such as transient receptor potential channels. These signals are then transmitted to the trigeminal brainstem sensory nuclear complex, with particular focus on the subnucleus caudalis, and the phenomenon of afferent convergence that is responsible for referred pain. The review highlights peripheral and central sensitization as the key amplifying mechanisms, neuroimmune and glial mechanisms sustaining these mechanisms and descending pathways that modulate nociceptive traffic. Special focus is on the transition from acute to chronic pain (chronification), maladaptive neuroplasticity, structural reorganization, and role of genetic, psychological and affective factors. A key contribution of this review is the integration of peripheral, central, neuroimmune, epigenetic and psychosocial mechanisms into a single mechanism-based framework of orofacial pain chronification specific to the trigeminal system, an integration that has not previously been assembled in this form. It is important to have a mechanism-based understanding of these processes in order to make an appropriate diagnosis, and for the development of individualized management of orofacial pain.

Keywords: Central Sensitization, Chronic Pain, Nociception, Neuroplasticity, Orofacial Pain, Trigeminal System.

Introduction

Orofacial pain conditions collectively affect a substantial proportion of the general population and are among the leading reasons for presentation to dentists, oral medicine specialists and primary care physicians. Beyond the physical burden of pain itself, these conditions frequently impair eating, speech, sleep and psychosocial functioning, and are associated with substantial direct and indirect healthcare costs. Because the trigeminal system subserves sensation from the teeth, oral mucosa, temporomandibular joint, masticatory muscles and much of the face and cranium, orofacial pain conditions span dental, neurological and psychiatric domains, and patients are frequently seen by multiple specialties before a mechanism-based diagnosis is reached.

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with, or reminiscent of, actual or potential tissue damage (1). This new definition explicitly distinguishes between the subjective experience of pain and a more objective neural process known as nociception, as pain is not a pure reflection of tissue injury. Now, however, the International Classification of Orofacial Pain (ICOP) provides a hierarchical framework for the classification of orofacial pain, similar to the headache classifications (2). The orofacial pain has a clinical character due to the anatomical density of innervation, representation in the brain and the specific organization of the brainstem that the trigeminal system has, when compared to the trunk and limbs (3). The gate-control theory of pain repurposed the perception of pain as an actively processed signal coming into the central nervous system, rather than the transmission of a signal along hardwired lines (4). This concept has now been expanded to model, in detail, at the molecular and systems level, how a transient

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noxious stimulus can, under certain conditions, become a sustained state of chronic pain.

This review deals with that pathway, from initial detection of the noxious stimuli at the periphery, to the processing, amplification and maladaptive central nervous system plasticity that leads to the chronification of pain, and will focus on orofacial-specific features.

Over the past two decades, a substantial body of work has characterised individual components of this pathway. Classic electrophysiological studies established the anatomical and functional organisation of the trigeminal brainstem sensory nuclear complex and demonstrated afferent convergence as the substrate of referred orofacial pain (5). Subsequent work defined central sensitization as a generalisable mechanism of pain amplification (6, 7), while later studies extended this framework to include glial and neuroimmune contributions (8, 9). More recent literature has begun to describe epigenetic regulation — DNA methylation, histone modification and non-coding RNA activity — as an additional layer that governs the durability of these sensitized states (10). However, much of this foundational literature was generated in spinal or generic somatosensory models, and comparatively few reviews have synthesised these mechanisms specifically within the anatomically and functionally distinct trigeminal system, where dense innervation, extensive afferent convergence across cutaneous, dental, visceral and muscular fields, and close coupling to autonomic and limbic circuitry produce a clinical picture that differs meaningfully from pain elsewhere in the body (3, 11). Existing narrative reviews of orofacial pain have also tended to describe either peripheral/central neurophysiology or clinical phenotypes in isolation, without an integrated account of how molecular, cellular, circuit-level and psychosocial processes combine across the trajectory from nociception to chronicity.

A clear gap therefore exists for a synthesis that traces this trajectory as a single continuum rather than as a set of disconnected mechanisms, and that situates emerging molecular findings — particularly epigenetic regulation and neuroimmune signalling — alongside the classical neuroanatomy of the trigeminal brainstem complex and its higher-order relays. The present review addresses this gap. Its overarching aim is to map the continuum from peripheral nociceptive transduction in the orofacial region to the establishment of persistent, centrally maintained chronic pain, using the trigeminal system as the organising anatomical and physiological framework. The specific objectives are:

(i) to describe the peripheral transduction mechanisms unique to orofacial tissues;
(ii) to detail the organisation of the trigeminal brainstem sensory nuclear complex, including the principal sensory nucleus and the subnuclei oralis, interpolaris and caudalis, and their afferent convergence onto wide-dynamic-range neurons as the anatomical basis of referred pain;
(iii) to outline the molecular and synaptic events of peripheral and central sensitization, including emerging epigenetic mechanisms;
(iv) to summarise the neuroimmune, glial and descending modulatory systems that sustain or resolve sensitized states; and
(v) to relate these mechanisms to the clinical spectrum of common orofacial pain disorders.

The novelty of this review lies in its integration of peripheral, central, neuroimmune, epigenetic and psychosocial mechanisms into a single mechanism-based framework of chronification that is specific to the trigeminal system, rather than extrapolated from spinal pain models, and in linking this framework directly to the differential diagnosis of common orofacial pain conditions for the practising clinician.

Methodology

This article is a narrative review of the neurobiological mechanisms underlying orofacial pain and its transition from acute nociception to chronicity. A literature search was conducted in the PubMed/MEDLINE, Scopus and Google Scholar databases for peer-reviewed publications in English. Search terms combined keywords such as orofacial pain, trigeminal, nociception, peripheral sensitization, central sensitization, neuroplasticity, chronic pain, glia and descending modulation. Foundational studies, authoritative reviews and recent primary reports addressing the peripheral, central, neuroimmune and psychosocial dimensions of trigeminal nociception were prioritized. Reference lists of retrieved articles were screened manually to identify additional relevant sources. Because the aim was to synthesize mechanistic

concepts across the nociception-to-chronicity continuum rather than to answer a single focused clinical question, a narrative rather than a systematic approach was adopted, and no formal risk-of-bias or quality scoring was performed. The selected literature was organized thematically to trace the pathway from peripheral transduction through central transmission, sensitization, chronification, neuroimmune modulation and individual vulnerability.

Regarding the reliability of data sources, priority was given to peer-reviewed original research and systematic or narrative reviews published in indexed journals with a defined editorial and peer-review process; conference abstracts, non-peer-reviewed preprints and non-indexed sources were excluded unless no peer-reviewed alternative existed for a specific mechanistic point. Foundational mechanistic studies published before 2020 were retained where they represent landmark or still-current evidence (for example, the original electrophysiological description of afferent convergence in the trigeminal subnucleus caudalis), while more recent publications from 2020–2025 were specifically sought to represent current understanding of emerging areas such as epigenetic regulation of nociception and the broader organisation of the trigeminal brainstem relay system. As with any narrative review, source selection was not exhaustive and carries a risk of selection bias, which is acknowledged as a limitation in the Discussion.

Results

Peripheral Nociception in the Orofacial Region

The process of nociception starts when a potentially harmful temperature, pressure and/or chemical change is detected by specialized primary sensory neurons, also known as nociceptors. In the orofacial region they are mainly thinly myelinated (Aδ) and unmyelinated (C) fibers, with cell bodies in the trigeminal ganglion. Transduction requires a family of membrane receptors and ion channels to transduce a wide variety of stimuli to depolarizing currents, and then requires voltage-gated sodium (Na^+) channels to generate action potentials and propagate them toward the brainstem (12). The capsaicin- and heat-sensitive transient receptor potential vanilloid 1 (TRPV1) channel is a molecular integrator of noxious heat and inflammatory signals, and a prototype of how a single receptor is coupled to the pain pathway (13).

The specialisation of orofacial nociception is seen in dental tissues. Almost all stimuli of sufficient magnitude are perceived as pain in the dental pulp and this property sets it apart from sensation in other parts of the body (14). Mediators released locally by tissue damage and inflammation sensitize peripheral nociceptor terminals: bradykinin, prostaglandins, protons, adenosine triphosphate (ATP) and nerve growth factor. Through this peripheral sensitization, pain thresholds are lowered and responsiveness is enhanced, leading to spontaneous pain and primary hyperalgesia common in acute pulpitis, mucositis and other inflammatory orofacial diseases (15).

Central Transmission and the Trigeminal Brainstem Complex

The trigeminal primary afferents make their connections with second-order neurons in the trigeminal brainstem sensory nuclear complex that includes the main sensory nucleus and the spinal tract nucleus with its subnuclei oralis, interpolaris and caudalis. The medullary dorsal horn (caudalis nucleus), which is structurally continuous with the spinal dorsal horn, is the main relay of orofacial nociceptive signals, and its laminar organization and connections to the thalamus and higher centres underlie the discriminative and affective aspects of orofacial pain (11).

Although the subnucleus caudalis has traditionally received the greatest attention because of its structural continuity with the spinal dorsal horn, the trigeminal brainstem sensory nuclear complex is not functionally limited to this subnucleus. The principal sensory nucleus and the more rostral subnuclei oralis and interpolaris also contribute to orofacial nociceptive and non-nociceptive processing, including a role of the interpolaris/caudalis transition zone in deep craniofacial and intraoral pain, and a contribution of subnucleus oralis to sensorimotor integration relevant to conditions such as temporomandibular disorders (11, 16). Beyond the brainstem complex itself, second- and third-order projections reach the parabrachial nucleus, which relays nociceptive and interoceptive information to the amygdala and hypothalamus and is thought to underlie the

strong affective and autonomic component of orofacial pain, before onward projection to thalamic and cortical structures (11). Viewing the trigeminal complex as a distributed, multi-nuclear relay rather than a single caudalis-centred station better accounts for the diversity of orofacial pain presentations and their frequent affective and autonomic accompaniments. Figure 1 depicts a schematic outline of the trigeminal nociceptive pathway from peripheral transduction to cortical and limbic processing, illustrating afferent convergence at the brainstem sensory nuclear complex and descending feedback.

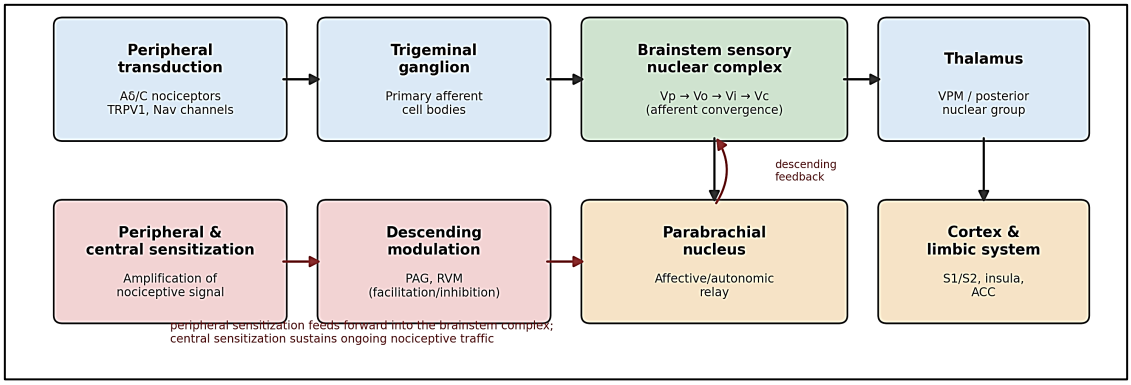

Figure 1: Schematic Outline of the Trigeminal Nociceptive Pathway from Peripheral Transduction to Cortical and Limbic Processing, Illustrating Afferent Convergence at the Brainstem Sensory Nuclear Complex and Descending Feedback

A prominent feature of the circuitry is that there is a great deal of afferent convergence. Sensory input in the subnucleus caudalis is from cutaneous, tooth pulp, visceral, neck and muscle afferents to individual nociceptive and wide-dynamic range (WDR) neurons. This convergence gives a neuroanatomical explanation for the poor localization, spread and referral of orofacial pain, such as cardiac pain referred to the jaw, or pulpal pain perceived across several teeth, and makes diagnosis of clinical cases more complicated (5).

Afferent Convergence and the Neurobiology of Referred Pain

The neurophysiological basis of this convergence is best explained by the convergence-projection theory, which proposes that nociceptive afferents from anatomically distinct tissues synapse onto the same second-order projection neuron in the subnucleus caudalis; because higher centres have no independent means of identifying which peripheral source activated that shared neuron, activity arising from a deep or visceral structure can be mislocalised to a cutaneous or dental site with an overlapping central representation (5). Wide-dynamic-range neurons are of particular importance in this process: unlike nociceptive-specific neurons, WDR neurons respond in a graded fashion to both innocuous and noxious stimuli across cutaneous, dental, muscular and even visceral afferents, and their multireceptive convergence makes them the principal substrate through which non-painful input can, under sensitized conditions, be read centrally as pain (17). During sustained nociceptive input, WDR neurons show expansion of their peripheral receptive fields and increased responsiveness to previously subthreshold or non-noxious stimulation - a phenomenon termed heterotopic facilitation — so that pain originating from one structure (for example, a pulpitic tooth) is perceived across an enlarged territory or in adjacent, uninvolved teeth and soft tissues (5, 17). Neurophysiological recordings in animal models confirm that a substantial proportion of caudalis WDR and nociceptive-specific neurons receive convergent input from cutaneous, dental, muscular, cervical and dural afferents, and that a subset project directly to the contralateral thalamus, providing a direct anatomical route by which convergent, centrally amplified signals reach conscious perception (5). This convergence-based mechanism accounts for well-recognised clinical phenomena such as cardiac pain referred to the jaw, pulpal pain perceived across several teeth, and the overlap between dental, muscular and headache-type orofacial pain presentations.

Peripheral and Central Sensitization

Central sensitization is an activity-dependent increase in excitability of central neurons that is produced by intense or prolonged nociceptive input. Substantially caused by glutamatergic signaling via N-methyl-D-aspartate (NMDA) receptors, coupled with intracellular signaling cascades, this state both increases synaptic efficacy and decreases inhibition and recruits into the neuronal response previously subthreshold inputs, such that a normal, or even innocuous, stimulus precipitates a painful response (6). From a clinical point of view, central sensitization presents with allodynia, hyperalgesia, increased receptive fields and the spread of tenderness beyond the injured site, and is now known to be a common mechanism shared by many acute and chronic pain conditions (7). The potentiation of nociceptive synapses is similar at a molecular level to long-term potentiation (LTP) of hippocampal synapses, and pain and memory share common features in their mechanisms of synaptic plasticity (9).

Mechanisms of Chronification: From Acute to Chronic Pain

Sensitization usually clears with healing of the tissue, and the system returns to its baseline. When these adaptive changes become entrenched and self-sustaining, they are said to be chronified. Pain after nerve injury can be maladaptive, occurring without any current tissue damage, and because of altered function of the somatosensory system (18). These injury discharges and molecular changes to the trigeminal ganglion neurons make them hyperexcitable, and this sensitization spreads to the subnucleus caudalis and upper cervical cord, leading to ectopic orofacial hypersensitivity and persistent orofacial sensitization (19). The orofacial region demonstrates some mechanisms different from spinal nerve injury, including those that are neuropathic, such as trigeminal neuralgia and persistent idiopathic facial pain (20). With chronic pain there is progressive structural and functional reorganization of the peripheral and central nervous system, for example changes in the connectivity of synapses and the representation of the cortex, which are related to the persistence and refractoriness of established pain (21).

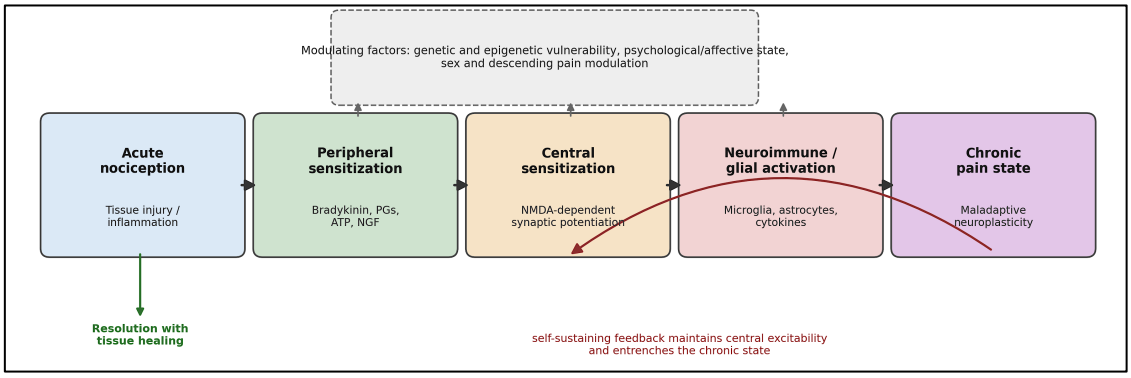

Figure 2: Transition From Acute Nociception to a Chronic, Self-Sustaining Orofacial Pain State, Showing the Modulating Influence of Genetic, Epigenetic, Psychological and Sex-related Factors

Epigenetic Regulation of Chronic Orofacial Pain

An additional, increasingly recognised layer of chronification operates at the level of gene expression rather than synaptic function alone. DNA methylation, histone acetylation and methylation, chromatin remodelling and non-coding RNAs (microRNAs and long non-coding RNAs) regulate the transcription of genes encoding ion channels, neurotransmitter receptors and inflammatory mediators within the trigeminal ganglion and brainstem complex, and these epigenetic marks are dynamically altered by peripheral inflammation and nerve injury (10). DNA methyltransferases and ten-eleven translon-cation demethylases modulate the balance of pro- and anti-nociceptive gene expression, and rapid DNA methylation reprogramming has been observed during the transition from acute to chronic pain states, implicating this process directly in chronification rather than merely as a downstream consequence of it (10). Because epigenetic modifications are, in principle, reversible, they are increasingly viewed as

candidate biomarkers of chronicity risk and as targets for pharmacological intervention, for example histone deacetylase inhibitors and RNA-based therapeutics. Direct evidence in orofacial pain models remains more limited than in spinal pain models; however, the shared molecular architecture of trigeminal and spinal nociceptive neurons makes it likely that comparable epigenetic mechanisms contribute to the chronification of orofacial pain, and this represents an important direction for future orofacial-specific research, as shown in Figure 2.

Neuroimmune and Glial Contributions

The common perception of pain as a problem with neurons alone has been expanded to include the role of non-neuronal cells. The satellite glial cells and infiltrating macrophages become activated following nerve injury and inflammation, and microglia and astrocytes become active in the subnucleus caudalis and upper cervical cord. Glial activation and the bidirectional neuron–glia communication it involves increase and preserve an excited state of neurons in orofacial pain (8). The neuro-inflammatory environment, which includes the release of cytokines, chemokines and growth factors (22), is now known to be a significant factor in central sensitization and the spread and chronicity of pain.

Descending Modulation of Nociception

Descending pathways from the periaqueductal gray, rostral ventromedulla and related brainstem regions continually regulate the trigeminal dorsal horn, both inhibiting and facilitating, as shown in Figure 3. Chronification results in an increased descending facilitation and a loss of descending inhibition, which actively contributes towards sustaining the pain state, while in the healthy state descending inhibition suppresses pain (23). In addition to cortical and limbic modulation, these modulatory systems are important targets for pharmacological and behavioural therapies and influence the craniofacial pain experience (24).

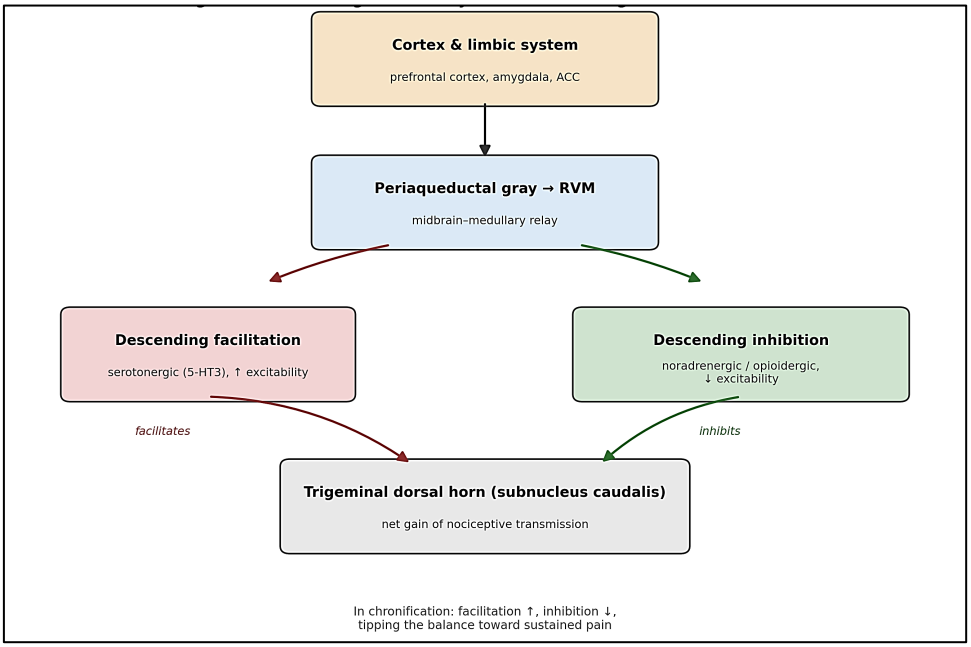

Figure 3: Descending Modulatory Control of the Trigeminal Dorsal Horn, Showing the Balance Between Facilitatory and Inhibitory Brainstem Outputs That Shifts Toward Net Facilitation During Chronification

Individual Differences and the Affective Dimension

The recovery and persistence of chronic orofacial pain depends on more than peripheral pathology. Often, chronic orofacial pain conditions have a high level of comorbidity with each other and with other disorders of body pain, the latter suggesting common vulnerability factors such as genetic, psychological and central amplification factors (25). There are hormonal, neural and social causes for the biological sex and gender differences in pain sensitivity and the prevalence of many orofacial pain conditions (26). The current perspective unites these various peripheral, central, immune and psychological components and suggests that the trigeminal sensory system is a plastic network that can serve both protective and pathological processes (27).

Clinical Spectrum of Common Orofacial Pain Disorders

The mechanisms described above converge, in varying combinations, on a heterogeneous group of clinical orofacial pain disorders that are frequently confused with one another and with pain of purely dental origin. Temporomandibular disorders reflect predominantly musculoskeletal nociception with a strong central sensitization component (28); trigeminal neuralgia is a paroxysmal neuropathic disorder typically attributed to vascular compression and focal demyelination of the trigeminal root (20); burning mouth syndrome is increasingly understood as a small-fibre and centrally mediated neuropathic disorder rather than a purely psychogenic one (29); persistent dentoalveolar pain disorder and post-traumatic trigeminal neuropathy both follow dental or surgical trauma but differ in their temporal and mechanistic profile (30); and migraine and cluster headache engage the trigeminovascular system and share partially overlapping, but distinct, brainstem and hypothalamic substrates (31). Table 1 summarises the principal mechanisms, typical clinical features and characteristic pain quality of these disorders to aid differential diagnosis.

Table 1: Clinical Spectrum of Common Orofacial Pain Disorders: Principal Mechanisms and Distinguishing Clinical Features

Disorder	Primary mechanism	Typical clinical features	Pain character	Reference
Temporomandibular disorders	Myofascial/joint nociception with central sensitization	Jaw/preauricular pain, limited or clicking jaw movement, muscle tenderness	Dull, aching, movement-related	(28)
Trigeminal neuralgia	Neurovascular compression, focal demyelination, ectopic firing	Paroxysmal unilateral attacks triggered by light touch, chewing or speaking	Brief, electric shock-like, severe	(20)
Burning mouth syndrome	Small-fibre neuropathy with central neuropathic dysregulation	Bilateral oral/tongue burning, often with dysgeusia and xerostomia sensation	Continuous burning, worsens through the day	(29)
Persistent dentoalveolar pain disorder	Central sensitization following dental trauma without ongoing pathology	Pain in a tooth or extraction site without identifiable dental cause	Dull, continuous, poorly localized	(30)
Post-traumatic trigeminal neuropathy	Peripheral nerve injury with ectopic discharge and central sensitization	Pain/sensory disturbance in the nerve distribution after surgery or trauma	Burning, tingling, allodynia	(30)
Migraine	Trigeminovascular activation, cortical spreading depression, CGRP release	Unilateral throbbing headache with photophobia/phonophobia, nausea	Pulsating, moderate to severe	(31)
Cluster headache	Hypothalamic dysregulation with trigeminal-autonomic reflex activation	Strictly unilateral periorbital attacks with autonomic signs (lacrimation, ptosis)	Excruciating, stabbing, circadian pattern	(31)

Summary of Key Molecular Mediators and Chronification Mechanisms

Because the mechanisms above involve numerous overlapping molecular players, Tables 2 and 3 summarise, respectively, the principal molecular mediators implicated in orofacial nociception and the key mechanisms that drive the transition from acute to chronic pain, to support rapid orientation for the reader.

Table 2: Key Molecular Mediators Implicated in Orofacial Nociception and its Chronification

Category	Representative examples	Principal role	Reference
TRP channels	TRPV1, TRPA1, TRPM8	Transduction of thermal and chemical noxious stimuli	(13)
Voltage-gated ion channels	Nav1.7, Nav1.8, Cav channels	Action potential generation and ectopic firing after injury	(12)
Neurotransmitter receptors	NMDA, AMPA, mGluR	Central sensitization and synaptic potentiation	(5)
Cytokines/chemokines	TNF-α, IL-1β, IL-6, CCL2	Neuroinflammation and glial activation sustaining sensitization	(9)
Neuropeptides	CGRP, substance P, PACAP	Neurogenic inflammation and trigeminovascular activation	(31)
Epigenetic regulators	DNMTs, TET enzymes, HDACs, microRNAs	Transcriptional control of pro- and anti-nociceptive genes	(10)

Table 3: Principal Mechanisms Contributing to the Chronification of Orofacial Pain

Mechanism	Anatomical level	Key feature	Reference
Peripheral sensitization	Nociceptor terminal	Lowered threshold and primary hyperalgesia	(15)
Central sensitization	Trigeminal brainstem complex	Synaptic potentiation and receptive field expansion	(6, 7)
Neuroimmune/glial activation	Trigeminal ganglion and brainstem	Cytokine release and bidirectional neuron–glia signalling	(8, 9)
Descending facilitation/ loss of inhibition	Brainstem–cortical loop	Net increase in nociceptive gain	(22)
Epigenetic reprogramming	Gene transcription	Durable, potentially reversible pro-nociceptive gene expression	(10)
Structural/cortical reorganization	CNS connectivity	Persistent pain representation and treatment refractoriness	(21)

Discussion

The literature reviewed here depicts orofacial pain not as a static symptom but as a dynamic continuum in which peripheral transduction, central transmission, sensitization, neuroimmune signaling and descending modulation interact to determine whether pain resolves or persists. The distinctive organization of the trigeminal system — its dense innervation, extensive afferent convergence and close coupling to affective and autonomic circuitry — shapes the characteristic clinical behaviour of orofacial pain, including its tendency to refer, spread and become centrally maintained. Viewing these mechanisms as an integrated network, rather than as isolated events, clarifies why some patients recover fully while others progress to chronic, treatment-resistant states.

The mechanism-based approach is clinically relevant. Physicians and dentists must be able to distinguish nociceptive pain of dental or musculoskeletal origin from neuropathic or centrally maintained pain in order to direct investigation and treatment appropriately, and to prevent inappropriate and sometimes irreversible dental treatment of teeth that are not the true source of pain (32). The role of peripheral

sensitization reinforces the importance of controlling inflammation at an early stage and at an effective level, while the evidence of central sensitization suggests that agents and strategies targeting central excitability, glial activation and descending modulation should address more than the periphery alone. Recognizing the path of chronification as preventable, rather than inevitable, reframes the treatment of acute orofacial pain as a chance to reduce the risk of chronic disability.

Recent evidence strengthens this mechanism-based view. Epigenetic reprogramming demonstrates that chronification is not simply a matter of prolonged synaptic signalling but also involves durable, and potentially reversible, changes in gene transcription within trigeminal ganglion and brainstem neurons (10), while detailed neuroanatomical mapping of the trigeminal brainstem complex confirms that nociceptive processing is distributed across the principal sensory nucleus and all three spinal subnuclei rather than confined to the caudalis alone (11, 16). Contemporary reviews of wide-dynamic-range neuron physiology further clarify how afferent convergence, established experimentally decades ago, remains directly relevant to modern accounts of referred and widespread orofacial pain (5, 17). Taken together with recent mechanistic work on temporo-mandibular disorders, burning mouth syndrome and post-traumatic trigeminal neuropathic pain (27-29), this literature reinforces the view that orofacial pain disorders that appear clinically distinct often share overlapping central mechanisms, which has direct implications for rational, mechanism-targeted rather than purely symptom-targeted treatment selection.

Conclusion

Orofacial pain is a continuum from the faithful detection of noxious stimuli by trigeminal nociceptors to persistent, self-sustaining chronic pain, mediated by peripheral, central and neuroimmune maladaptive plasticity. All of these mechanisms contribute to the acute and chronic presentations observed in clinical practice, and the special organization of the trigeminal system, the convergence that leads to referred pain, the amplifying effect of peripheral and central sensitization, and the modulatory effect of glia and descending pathways together shape them. Realizing better outcomes requires translation of this understanding of the underlying neurobiology into mechanism-based diagnosis and individualized treatment, and continued research into the factors that govern the progression from nociception to chronicity.

This review's principal contribution is to draw the peripheral, central, neuroimmune, epigenetic and psychosocial strands of this literature into a single mechanism-based framework specific to the trigeminal system, and to relate that framework directly to the differential diagnosis of common orofacial pain disorders, as given in Table 1. The clinical consequence of this framework is a shift away from treating orofacial pain as a purely local or purely dental problem and toward earlier recognition of features suggesting sensitization or neuropathic involvement, which may allow intervention before pain becomes centrally entrenched. Several limitations should be acknowledged: as a narrative rather than a systematic review, the selection of literature was not exhaustive and is subject to selection bias; much of the mechanistic evidence, particularly regarding epigenetic regulation, is derived from spinal or generic somatosensory models and has not yet been fully validated in orofacial-specific systems; and the review does not provide a systematic quantitative synthesis of treatment efficacy. Future research should prioritise trigeminal-specific studies of epigenetic and neuroimmune mechanisms, longitudinal studies identifying which patients with acute orofacial pain are at greatest risk of chronification, and validation of imaging or molecular biomarkers that could support earlier mechanism-based diagnosis and individualized treatment selection in clinical practice.

Abbreviations

ATP: adenosine triphosphate; IASP: International Association for the Study of Pain; NMDA: N-methyl-D-aspartate; TRPV1: transient receptor potential vanilloid 1; WDR: wide-dynamic range. DNMT: DNA methyltransferase; TET: ten-eleven translocation enzyme; HDAC: histone deacetylase; CGRP: calcitonin gene-related peptide; PACAP: pituitary adenylate cyclase-activating polypeptide.

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Author Contributions

Riya Parwani: conceptualization, literature review and manuscript writing. Akshay Katara: literature review and manuscript writing. Sheetal Gajra: critical review and editing of the manuscript. Rubina Sarah Amin: critical review and editing of the manuscript. Fancy Christina Kumraraja: critical review and editing of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

Data Availability

Data sharing is not applicable to this article, as no new data were created or analyzed in this review.

Declaration of Artificial Intelligence (AI) Assistance

During revision of this manuscript in response to peer review, an AI-based language model (Claude, Anthropic) was used to assist with literature retrieval, drafting of expanded text, generation of the schematic figures (Figures 1–3), and reference formatting. All AI-assisted content was critically reviewed, verified against the cited primary and secondary sources, and edited by the authors, who take full responsibility for the scientific accuracy, originality and integrity of the final manuscript.

Ethics Approval

Ethical approval was not required, as this is a review of previously published literature and did not involve human participants or animals.

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