Review Article

Idiopathic orofacial and nociplastic pain in elderly patients: a narrative review

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Background and Objective: Idiopathic orofacial pain (IOFP) includes burning mouth syndrome (BMS), persistent idiopathic facial pain (PIFP), and persistent idiopathic dentoalveolar pain (PIDAP). We aimed to perform a narrative review on the role of nociplastic pain mechanisms in IOFP in elderly patients.

Methods: We conducted a PubMed search using only English for studies published between April 1990 and March 2020 on IOFP and nociplastic pain using the following search terms: "(Burning Mouth Syndrome OR Persistent Idiopathic Dentoalveolar Pain OR Atypical Odontalgia) AND (Temporal Summation OR Conditioned Pain Modulation OR Quantitative Sensory Testing) AND (1990/04/01:2021/9/01[Date - Entry])".

Key Content and Findings: We identified 43 potentially relevant articles, and upon review selected 13 studies for this review; 9 were for BMS, and 4 were for PIDAP or atypical odontalgia. The IOFPs are caused by a decrease in the function of descending pain inhibition. Conditioned pain modulation (CPM) represents a natural inhibitory process on pain, which decreases with age in the orofacial region. Reduced CPM may be one of the reasons for the increased prevalence of chronic pain in older individuals. Lack of brain structures or dysregulation in the endogenous opioid system could also be a factor in the lack of the CPM effect in older individuals.

Conclusions: this review implies the idiopathic oral pain syndromes may have more nociplastic pain components than psychogenic pain. Future research is needed to further assess the relationship between nociplastic pain and psychogenic pain on the orofacial regions.

Keywords: Burning mouth syndrome (BMS); persistent idiopathic dentoalveolar pain (PIDAP); descending pain inhibition; nociplastic pain

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Introduction

Idiopathic orofacial pain (IOFP) includes burning mouth syndrome (BMS), persistent idiopathic facial pain (PIFP), and persistent idiopathic dentoalveolar pain (PIDAP). The International Classification of Orofacial Pain defines BMS as "an intraoral burning or dysesthesia sensation, recurring daily for more than two hours per day for more than three months, without clinically evident causative lesions" (1). It is

usually felt in the tip of the tongue, tongue rim, and palatal mucosa. BMS is most prevalent in elderly females. PIFP is defined as "persistent facial pain of various characteristics, recurring daily for more than two hours per day for more than three months" (1). PIDAP which has been redefined most recently (ICOP, 2020), is characterized by persistent deep, dull, or pressure-like pain in the tooth or alveolar bone in the absence of local causes. Each of the IOFPs are classified into those with and those without somatosensory abnormalities. Somatosensory abnormalities can be positive (hypersensitivity) or negative (dulled sensations) symptoms. However, unlike neuropathic pain, the region of sensory abnormalities is not limited to the area controlled by the trigeminal nerve (2).

Traditionally, pain mechanisms have been divided into "nociceptive" and "neuropathic" categories, neither of which adequately describe IOFPs. The term "nociplastic pain" was introduced by the International Association for the Study of Pain (IASP) in 2017 as a third mechanistic pain descriptor (3).

It has recently been reported that IOFP includes an element of nociplastic pain that represents a modulation in somatosensory processing, such as the dysfunction of descending pain inhibition (2). Temporal summation (TS) and conditioned pain modulation (CPM) has been observed using a novel intraepidermal electrical stimulation (IES) process in patients with BMS and in healthy adults. There is growing recognition that not only changes in peripheral neurons but also changes in central neurons may be involved in the development of PIFP, suggesting the presence of neuropathy components (4-7). Regardless of the generator of peripheral pain, PIFP has been suggested to occur due to a central phenomenon/amplification caused by processes that occur in the periphery. Similar to those shown in fibromyalgia (8), low back pain (9), and peripheral neuropathic pain (10).

Objectives

This narrative review was conducted to address the following focus question: does IOFP include an element of nociplastic pain that represents a modulation in somatosensory processing? In this review, IOFP and nociplastic pain that occur in elderly patients are discussed. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-96/rc).

Methods

Research selection

This narrative review was conducted based on the following focus question: Does IOFP, such as BMS or PIDAP, include an element of nociplastic pain that represents a modulation in somatosensory processing?

A literature search in PubMed was performed for studies from April 1990 to March 2020. The search keywords included "(Burning Mouth Syndrome OR Persistent Idiopathic Dentoalveolar Pain OR Persistent Idiopathic Facial Pain OR Atypical Odontalgia) AND (Temporal Summation OR Conditioned Pain Modulation OR Quantitative Sensory Testing) AND (1990/04/01:2021/9/01[Date - Entry])".

A total of 43 studies were retrieved in PubMed. According to the question in this narrative review, 13 studies were selected; 9 on BMS and 4 on PIDAP or atypical odontalgia (*Table 1*).

Discussion

Nociplastic pain

The IASP introduced the concept of nociplastic pain in 2018 as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (11). Therefore, nociplastic pain is a pathological condition wherein a patient has abnormally heightened sensitivity to peripheral stimuli manifesting as allodynia (a somatosensory abnormality in which non-noxious stimuli are perceived as painful) and hyperalgesia (amplification of pain stimuli) in the absence of any local pain-causing disease or disorder. These abnormal amplifications of peripheral stimuli are characteristically observed in neuropathic pain (12) but can also be observed in nociplastic pain (13); however, tissue or nerve damage in the peripheral tissues resulting in pain is observed only in neuropathic pain. When noxious stimuli do not actually originate from peripheral and nerve tissues, the central nervous system amplifies pain or recognizes it with abnormally heightened sensitivity in patients with nociplastic pain. It is believed that the pain regulation mechanism in the brain, especially descending pain inhibition, is modulated, resulting in an overreaction to non-noxious input from the periphery (13).

A previous study has shown that CPM is reduced in

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	September 1, 2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)*	(Burning Mouth Syndrome OR Persistent Idiopathic Dentoalveolar Pain OR Atypical Odontalgia OR Persistent Idiopathic Facial Pain) AND (Temporal Summation OR Conditioned Pain Modulation OR Quantitative Sensory Testing)
Timeframe	(1990/04/01:2021/9/01[Date - Entry])
Inclusion and exclusion criteria (study type, language restrictions etc.)	We included review articles, meta-analyses, and original studies published in English. We excluded case reports, protocols, short communications, personal opinions, letters, conference abstracts, or laboratory research
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	NN and ZY independently screened the full-text articles, with disagreements being resolved through consensus with KU, YT, CS and AY

*, please use an independent supplement table to present detailed search strategy of one database as an example.

older individuals (14). Recently, Khan *et al.* demonstrated that CPM in both the right and left gingival sites decreases as age increases (15). Reduced CPM may be one of the reasons for the increased prevalence of chronic pain in older individuals (16). It has been reported that in the absence of the descending pain inhibitory system, noxious stimuli can be perceived as pain (15). The lack of brain structures or dysregulation in the endogenous opioid system could also be a factor in the decrease of CPM in older individuals. The neural and hormonal pain-modulatory systems are gradually influenced by the aging process along with the loss of noradrenergic and serotonergic fibers in the spinal dorsal horn and decline of the opioid system

Nociplastic pain and BMS

When selective C-fiber stimulation is repeatedly applied to the orofacial region, neuronal excitement rapidly increases due to the input signal of the pain stimulus, and a windup phenomenon occurs in the caudal subnucleus of the trigeminal spinal tract. N-methyl-D-aspartate (NMDA) receptors, on which glutamic acid acts as an excitatory neurotransmitter, are involved in the windup phenomenon (17). Previous studies have reported that TS can be induced by applying repeated noxious thermal stimuli to the forearms of patients with BMS (18). When repeated electrical stimulation (10 stimuli at 1 Hz) was applied to the lips of patients with BMS and healthy adults, the pain intensity with each stimulus after 10 stimulations was higher than that after the first stimulation, suggesting that TS was induced. However, this excessive activation of NMDA receptors is not exclusive to the pathophysiology of BMS, as the windup phenomenon was also observed in healthy adults (19).

CPM is a phenomenon wherein pain inhibits pain. A noxious stimulus [conditioning stimulus (CS)] at a distant site inhibits wide-acting neurons in the posterior horn of the spinal cord or the caudal subnucleus of the trigeminal spinal tract via the brain stem, thereby inhibiting pain transmission (test stimulus). It has been reported that CPM is attenuated in patients with conditions that cause chronic pain such as fibromyalgia, irritable bowel syndrome, chronic tension headaches, and migraine (20,21).

CPM of a 40 ℃ CS was reported to be similar in patients with BMS and healthy adults, although CPM of a 47 ℃ CS was significantly decreased in patients with BMS compared to that in healthy adults (19). These results suggest that the pain control mechanism works similarly in patients with BMS and in healthy adults in response to non-noxious CS but not with noxious CS (19).

Psychological factors such as anxiety and depression may explain some of the individual variability in pain perception and therefore may also play a role in CPM, possibly due to the fact that serotonin and noradrenaline are involved in both anxiety and depression are involved in the CPM response. Recently, Ozasa *et al.* found a significant positive correlation of CPM 47 ℃ with state and trait anxiety in patients with BMS, suggesting that both state and trait anxiety negatively affect the descending pain modulation system (22).

In patients with BMS, paresthesia increased tongue pain

when hot food and drinks were consumed. Shinozaki *et al.* analyzed the brain function of patients with BMS using functional magnetic resonance imaging (fMRI) (23). When noxious heat stimuli were applied to the lips of patients with BMS, strong activity in the pain matrix, which includes the anterior cingulate gyrus, insular cortex, and prefrontal cortex, was detected. In contrast, when noxious heat stimuli were applied to the lips of healthy adults, habituation was observed. In healthy adults, the descending pain inhibition circuit suppresses activity in the cerebral cortex (anterior cingulate gyrus). Repeated noxious stimuli resulted in pain habituation, which affected the way pain was felt. However, in patients with BMS, this habituation was not observed. This lack of descending pain inhibition may lead to diminished pain habituation (23).

In a study by Watanabe *et al.* using somatosensory testing, they revealed that elderly patients with BMS had significantly higher cold pain thresholds (CPTs) than healthy adults, and that sex hormones influenced cold and pain perception (24). The neuroprotective and nerve regeneration ability of sex hormones, and the fact that rapid changes in sex hormones during menopause damage small diameter fibers (Aδ) and cause cold hyperalgesia, are thought to play a role in the modulation of CPT (25). Yilmaz *et al.* reported that Aδ fibers are more susceptible to damage than C fibers in patients with BMS and may induce central sensitization (26). Cold stimulation can be used to differentiate central sensitization in patients with chronic oral pain (27).

Wada *et al.* examined resting brain fMRI images in patients with BMS and healthy adults and found that the functional connections of the prefrontal cortex and orbitofrontal area, anterior cingulate gyrus, basal ganglia, thalamus, and brain stem were strengthened in patients with BMS (28). These sites are similar to the dopaminergic nerve fiber pathways involved in descending pain modulation. Morissette *et al.* reported that the administration of 17-estradiol or progesterone to animals in which the ovaries had been extracted increased dopamine uptake in the striatum (29). When pain is induced in healthy adults, increased binding of dopamine antagonists to the D2 receptors of the caudate nucleus, putamen (30), and striatum (31) occurs according to the pain intensity. Furthermore, binding to the nucleus accumbens increases depending on emotional factors (32). However, the uptake of F-dopamine in the putamen is lower in patients with BMS than in healthy adults (33). The reactive increase of dopamine transmission in the basal ganglia in response to the stresses of pain and emotion observed in healthy patients is suppressed in patients with BMS. CPM has been reported to be significantly enhanced when dopamine agonists are subcutaneously injected compared to when placebos are used, which may help explain the decreased CPM among patients with BMS. Furthermore, the amount of dopamine in the basal ganglia is significantly reduced in patients with untreated depression compared to healthy adults (34), suggesting that emotions may affect the dopaminergic nervous system in patients with BMS.

In contrast, brain stimulation therapy, such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation, was reported to be effective for patients with primary pain syndromes who present with nociplastic pain, including those with fibromyalgia, complex regional pain syndrome, and BMS (35-38). Additionally, dopamine release in the striatum increased in brains that underwent electroconvulsive therapy (39). However, more research is needed to identify effective treatments for chronic primary pain.

Nociplastic pain and PIDAP

PIDAP was first reported in 1,778 and is characterized by persistent pain in one tooth or at a site of tooth loss (dental alveolus) with no usual dental cause (40). Due to its unclear pathophysiology, PIDAP has previously been described as idiopathic periodontalgia, phantom tooth pain, atypical odontalgia, idiopathic toothache, post-traumatic painful trigeminal neuropathy, and persistent dentoalveolar pain disorder (12).

In the 2018 International Headache Classification, 3rd Edition (2), atypical odontalgia was listed as "a subtype of persistent idiopathic facial pain (PIPF)" under classification 13.12. PIPF is defined as persistent facial and/or oral pain with a variety of symptoms and poor localization, and most patients are female. In contrast, atypical odontalgia is clearly localized, has an early age of onset, and has no significant prevalence difference between sexes. In addition, PIFP is listed in category 6.2 of the International Orofacial Pain Classification, 1st Edition in 2020 (11), while pathological conditions previously referred to as atypical odontalgia are listed as PIDAP in category 6.3. As such, the two diseases are classified separately.

The pathophysiology of IOFP may include central sensitization and modulation of pain processing in the brain. Studies using brain functional imaging suggest that IOFP may be amplified during central pain processing, similar

to the amplification of pain in fibromyalgia and irritable bowel syndrome (41). Woda *et al.* suggested that higher pain centers are involved in IOFP, and that the addition of emotional stress and peripheral stimuli to biochemically and psychologically vulnerable patients lead to increased neuropeptide levels in the target tissues, leading to disease development (42). Some patients with IOFP may present with paresthesia with warm or cold stimuli, pin pricks, or mild tactile stimuli on clinical somatosensory exams. IOFP can also be accompanied by modulation of the somatosensory nervous system and may be related to modulation of the descending inhibitory system and nociplastic pain (2). Nasri-Heir *et al.* reported that CPM in patients with idiopathic persistent odontalgia was decreased compared to that in healthy adults, and that CPM was significantly attenuated in patients with brain disease of one year or longer (43). In addition, a relationship between CPM and post-root canal treatment has been reported (44). Patients with endodontic diseases underwent CPM evaluation prior to root canal treatment, and patients with low CPM had a high risk of developing chronic orofacial pain, and patients with higher CPM before treatment had less chronic pain 6 months postoperatively. These results suggest that CPM can be used to evaluate the endogenous analgesic system in patients with nociplastic pain (44).

This review has a limitation. Compared to PIFP, there were less studies on sensory changes, CPM, or MRI related to PIDAP in this region. The few studies on PIDAP may be attributed to the fact that PIDAP has a component of neuropathic pain as it is more common after receiving root canal treatment. Further research will be needed to elucidate the pathophysiology of PIDAP.

Summary

The idiopathic oral pain syndromes that were previously considered to be psychogenic pain are now considered as nociplastic pain components that are part of the chronic primary pain syndrome. Although the exact cause of pain is unknown, there is central dysregulation in information processing of peripheral stimuli in nociplastic pain. In particular, descending pain inhibition is impaired, resulting in pain amplification. Dysfunction of the dopaminergic nervous system plays a key role in nociplastic pain in the oral region.

It is important to recognize that nociplastic pain, unlike nociceptive pain and neuropathic pain, may be amplified by central nervous system conditions, such as fatigue, inadequate sleep, memory, mood anxiety and depression problems. Consistent with this central component, this type of pain does not typically respond to peripherally-directed therapies such as anti-inflammatory drugs and opioids, surgery, or injections.

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Footnote

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