



# Taste changes in orofacial pain conditions and coronavirus disease 2019: a review

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**Background and Objectives:** Taste sensation has a significant evolutionary, nutritional and protective role in human beings. Changes in the perception of taste can significantly affect the overall quality of life of an individual. A significant proportion of patients with taste changes such as ageusia (complete loss of taste), hypogeusia (diminished taste sensation), dysgeusia (altered/distorted taste sensation including taste phantoms like metallic/bitter taste) present to the dental and medical healthcare professionals. The objective of the narrative review is to familiarize healthcare professionals with taste changes in orofacial pain conditions and coronavirus disease 2019. The manuscript objective of the narrative review is to familiarize the dental and medical healthcare professionals with the taste pathway and pathophysiological mechanisms, diagnostic testing and management.

**Methods:** Indexed databases (PubMed, EMBASE, Scopus, ISI Web of Knowledge, Medline, OVID, Scopus, Cochrane library) were searched using the keywords “Taste”, “Taste changes” from 1918 to 2020.

**Key Content and Findings:** Taste changes may occur as a consequence of normal physiological changes or secondary to pathology. Taste alterations secondary to pathology encompasses various local, systemic factors such as coronavirus disease 2019 (COVID-19), burning mouth syndrome (BMS) and damage or disease of the peripheral or central nervous system (CNS). BMS is one of the most enigmatic and poorly understood orofacial pain condition. Significant proportion of the patients with BMS present with taste changes, taste phantoms, subjective oral dryness and burning sensation. Various local and systemic factors such as local irritants (chemical/mechanical), mucosal lesions, radiation therapy, medications, iatrogenic injury, deficiencies, infections (bacterial, fungal, viral), trauma, endocrine, neuromuscular and autoimmune disorders may induce changes in taste. Taste loss may be a key cardinal clinical feature associated with the COVID-19. The manuscript aims to familiarize the dental and medical healthcare professionals with the taste pathway and pathophysiological mechanisms, diagnostic testing and management.

**Conclusions:** A variety of physiological and pathological conditions (local and systemic) may induce changes. Identifying the underlying pathophysiological mechanisms and multidisciplinary management are the keys to success.

**Keywords:** Taste; taste pathway; COVID; orofacial pain

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## Introduction

Taste is one of the primordial sensations with an important role in nutrition and survival instincts of an organism. Changes in taste perception are reported to occur in approximately 0.6–7.2% of the adult population (1,2). The variations in the prevalence of taste changes may be attributed to differences in the study population, criteria, and methods used to assess taste alterations. Age and sex related differences have also been reported in the prevalence of taste changes. An epidemiological study by Bergdahl *et al.*, estimated the prevalence of taste changes in 2.5% of the subjects assessed (0.9% in males and 3.8% in females) (3). The study also reported variations in the prevalence of taste changes among groups stratified based on the age (second to the sixth decade) and in males and females; males (no cases were reported in the second and sixth decade, 1.9% in the third decade and 1.8% in the fourth decade) and females (1% the second decade, 3.8% in the third decade and increasing to 5.1% in the sixth decade (3). Taste changes are often distressing to the patients and affect their quality of life (4,5).

Alterations in taste may be physiological or secondary to local, systemic factors such as coronavirus disease 2019 (COVID-19) and syndromes such as burning mouth syndrome (BMS). Taste changes may be qualitative or quantitative. Quantitative changes in taste such as ageusia (complete loss of taste), hypogeusia (diminished taste sensation), hypergeusia (enhanced perception of taste) and qualitative changes such as dysgeusia (altered/distorted taste sensation) and phantogeusia (taste phantoms like metallic/bitter taste in absence of stimulation) (6). A significant proportion of patients with taste changes present to the dental and medical healthcare professionals. Taste phantoms in the absence of any stimulation are a significant source of distress to patients. The review aims to familiarize dental and medical healthcare professionals with physiological and common pathophysiological mechanisms which can induce changes in taste and briefly discuss diagnosis and management strategies.

## Methods

Indexed databases (PubMed, EMBASE, Scopus, ISI Web of Knowledge, Medline, OVID, Scopus, Cochrane library) were searched using the keywords (“taste”[MeSH Terms] OR “taste”[All Fields] OR “tastes”[All Fields] OR “tasting”[All Fields] OR “tasted”[All Fields] OR “tasteful”[All Fields] OR “tastings”[All Fields]) AND

(“change”[All Fields] OR “changed”[All Fields] OR “changes”[All Fields] OR “changing”[All Fields] OR “changings”[All Fields]) AND (“taste”[MeSH Terms] OR “taste”[All Fields] OR “tastes”[All Fields] OR “tasting”[All Fields] OR “tasted”[All Fields] OR “tasteful”[All Fields] OR “tastings”[All Fields]) from January 1st 1918 to October 31st 2020 independently by 2 authors (JK, MK). In case of disagreement, a consensus was obtained by discussion and involving a third author (NN). Research studies, clinical trials, randomized controlled trials, case reports, books, documents, narrative reviews, systematic reviews and meta analysis in English were included. Letters to the editor, commentaries were excluded.

## Taste pathway

Taste sensation is complex and encompasses both the innate and learned components (7). Sensory perception for taste has been identified for at least five different modalities including sweet, sour, salt, bitter and umami. Recently, taste receptors for fat have been identified and considerable debate exists on whether fat should be considered an additional taste sensation or if it plays just a role in modifying other tastes such as umami (8). Tongue maps describing specific areas of the tongue for different tastes are now considered to be redundant (9). Current findings suggest that all areas of the tongue are capable of perceiving different taste sensations but some areas are more specific.

Taste sensation from the anterior 2/3rd of the tongue is carried by the chorda tympani nerve (a branch of the facial nerve), posterior 1/3rd by glossopharyngeal nerve and epiglottis by the vagus nerve. Taste sensation from the palate is carried by the greater petrosal nerve, a branch of the facial nerve. Lingual nerve (a branch of the trigeminal nerve) is the general sensory afferent (10). The perception of taste is initiated by the dissolution of molecules and activation of various taste receptors (11). Taste receptors are present on taste cells located within the taste buds. Four types of taste cells Type I–IV have been identified; Type I (similar to astrocytes), Type II (respond to sweet, bitter, umami), Type III (sour and salty) and Type IV (immature cells). Each taste cell is specific to a particular taste; however, taste buds have multiple taste cells (each of which may respond to a different taste) and are thus nonspecific (8). Taste buds are thus capable of responding to more than one taste. Taste buds are located primarily in the fungiform papilla and to a lesser extent on the circumvallate and foliate papilla (12,13). Fungiform papillae have been

shown to contain multiple taste buds and each taste bud is encircled by afferent neurons transmitting pain sensation in a basket like formation. The taste buds are distributed at various sites in the alimentary canal; predominantly in the epithelium of the dorsum of the tongue and to a lesser extent in the palate, pharynx, superior third of esophagus and epiglottis. Studies have reported taste receptors in the gut and nasal passages as well (14-16).

At the receptor level in the taste buds, chemical signals from the various molecules are transduced to electrical signals which are carried from the peripheral nervous system (PNS) to the central nervous system (CNS) by the afferent nerves. During the process of transduction, Type II taste cells utilize G protein-coupled receptors with ATP as the primary neurotransmitter; Type III cells use voltage gated calcium channels and 5-HT as the primary neurotransmitter (8). Following transduction, the afferent impulses relay to the nucleus tractus solitarius (NTS) and from there they synapse at the thalamus and proceed to the somatosensory cortex. Variations have been described in the projection pathway of the second order neurons to the thalamus and somatosensory cortex. The second order neurons from NTS synapse at the thalamus and a majority project to the ipsilateral cerebral cortex; few may cross to opposite side and project to the contralateral cerebral cortex and on rare occasions few fibers may have bilateral representation (10,17-19). Taste sensation is finally interpreted by the primary and secondary taste centers of the insular cortex (20). Imaging studies have shown that taste sensation for sweet and salt are readily distinguishable, however bitter taste is associated with an avoidance behavior causing deactivation of the primary gustatory complex as a protective response (21).

The final perception of taste involves integration of multiple somatosensory and olfactory modalities (7). The pathways for smell and taste frequently interact. In addition to the activation of taste receptors, the touch receptors present in the oral cavity are also activated on consumption of food and enable localization of taste. Following the dissolution of molecules in food, the volatile components also stimulate the olfactory receptors which are located on the roof of the oral cavity through retro nasal olfaction leading to smell and recognition of food (7).

### **Taste changes and physiological variations**

Taste changes may be result of physiological factors like aging, pregnancy, menopause, ethnic and genetic variations.

Elderly subjects report a decrease in salt and bitter taste acuity (22,23) and elevated taste threshold (24). Age related changes, hyposalivation, co morbid medical conditions, concurrent medications (3), vitamin and mineral deficiencies may play a role in inducing taste alterations in elderly. Taste changes especially bitter taste perception are frequently reported in pregnant females with complaints of hyperemesis (25) which is more pronounced in the first trimester. According to Duffy *et al.*, this may be a normal protective mechanism to prevent ingestion of poisonous substances which have a bitter taste (26). Genetic and ethnic variations have also been reported with higher taste sensations among Hispanics and African Americans (27).

### **Taste and pain**

Taste mediated suppression of pain may also be related to central mechanisms. Sucrose mediated suppression of pain occurs rapidly and lasts for a very short period (few minutes) (28,29). This effect was suggested to be naltrexone dependent in rats (29,30) and in humans (31,32), suggesting opioid dependency of the mechanism. Centers involved in opioid dependent pain [rostral ventromedial medulla (RVM) and the periaqueductal gray (PAG)] (33,34) mediate pain suppression via descending pathways. Study has shown that Fos expression was induced in the PAG and RVM following sucrose administration (35).

### **Taste and BMS**

The International Classification of Orofacial Pain (ICOP) defines BMS as “An intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day for more than 3 months, without evident causative lesions on clinical examination and investigation” (36). The diagnosis is based on exclusion of local and systemic factors which cause burning sensation. BMS was previously referred to by various terminologies such as glossodynia, glossopyrosis, oral dysesthesia, primary BMS, idiopathic BMS and stomatodynia (36,37). Majority of the epidemiological studies especially the older ones are flawed with the lack of clear diagnostic criteria, poor methodology and failure to distinguish BMS from BMSs. This has resulted in wide variations in the estimated prevalence of BMS from 1–15% (38). The condition has a female predominance and has the highest prevalence in the 5th and 6th decade (38,39). The intensity of pain in BMS varies from mild to severe, and may be continuous/intermittent at single

or multiple sites in the oral and perioral structures (most common is the tongue followed by palate, lips, buccal mucosa). Majority of the cases present with symmetric bilateral involvement of affected structures (20). Pain often amplifies as the day progresses; but does not interfere with the sleep. BMS patients often report subjective somatosensory changes such as taste changes, taste phantoms, hypo salivation, and improvement in pain with consumption of sweet food (39,40). It is estimated that 11-68% of patients with BMS report taste dysfunction (41-44) and approximately 2/3rd of the patients report subjective xerostomia, and dysesthesia (36). Approximately 1/3 of post-menopausal women (42) report taste changes and it is predominant in patients experiencing a combination of dysgeusia, burning/pain and oral dryness.

Symptoms of burning sensation in the oral and perioral structures may be secondary to local (trauma from intraoral prosthesis such as dentures, candidiasis, xerostomia, contact allergy, post radiation/chemotherapy mucositis, and mucosal lesions such as aphthous ulcers, lichenoid reactions, herpes) and systemic factors such as diabetes, autoimmune disorders such as Sjogren's syndrome, lichen planus, vitamin and micronutrient deficiencies (niacin, iron, vitamin B-12, or folic acid, zinc), hypothyroidism, medications (e.g., ACE inhibitors), gastro esophageal reflux disease (45). Burning symptoms secondary to local and systemic factors was previously referred to as secondary BMS (37). Taste changes are frequently seen in many BM conditions. Distinction between BMS and BM is crucial for successful treatment. Treatment of the underlying pathologies results in complete resolution of symptoms in patients with BM. Taste changes associated with burning mouth have been described in the section of taste changes secondary to local and systemic factors (*Table 1*).

### *Theories of taste changes in BMS*

#### **Disinhibition theory**

Mounting evidence from animal and human studies suggests that taste sensation specifically sweet sensation has the ability to inhibit pain (28,57-61) ipsilaterally to contralaterally (62). When one nerve innervating taste is damaged its inhibitory effect on another is lost. This often results in taste phantoms (9), intensification of pain and pain/oral burning. It has been shown that topical application of local anesthetic may enhance burning sensation in patients with BMS (63). The intensification of pain by inhibiting/anesthetizing one nerve supports the previously

proposed disinhibition theory. Disinhibition theories have also been supported by quantitative sensory testing (QST) which has shown chorda tympani hypofunction (45,64-67).

#### **Supertaster theory**

In 1931, Fox accidentally discovered that he could not taste phenylthiocarbamide (PTC) while his colleague observed a bitter taste. A subsequent evaluation of 2,500 participants revealed that 28% could not taste PTC (referred to as non-tasters); 65.5% observed bitter taste (referred to as tasters); and the rest, reported other taste qualities (68). Fisher later suggested replacement of PTC by 6-n-propylthiouracil (PROP) as it is odorless and less toxic (69). Tasters have been further subclassified into moderate tasters (who perceive PROP to be moderately bitter) and supertasters (who perceive PROP to be severely bitter) (70) based on their perception of taste to PTC/PROP. Genetic variations underlying inability to taste may be related to the number of taste buds and fungiform papillae; with non-tasters having the least number of fungiform papillae and supertasters exhibiting up to four times the number of taste buds compared to non-tasters and exhibiting densely packed smaller fungiform papillae (9,12).

The fungiform papillae have multiple taste buds encircled by afferent neurons transmitting pain sensation in a basket like formation (67). Hence, supertasters exhibiting increased number of fungiform papillae also have an increased number of pain transmitting neurons and a greater predisposition to enhanced perception of oral pain (67,71,72). Contradictory results exist on whether the oral burning is proportional to the density of fungiform papillae with some studies suggesting an association and others refuting the claim (67,73). Family studies have suggested that inability to taste PTC is a mendelian recessive trait (two recessive alleles "tt") and tasters have one dominant and one recessive or two dominant alleles (Tt/tT or TT) (68). The PROP gene has been localized to chromosome 5 and a region on chromosome 7 (74). Females are more responsive to PTC/PROP (12). However, caution should be excised in the classification of tasters *vs.* non-tasters as pathologies (hypothyroidism, head injury etc.) may frequently enhance or reduce the perception of taste to PROP and result in misclassification of the groups (75).

#### ***Role of gamma-aminobutyric acid (GABA) in taste inhibition***

GABA is an inhibitory neurotransmitter found in the taste

**Table 1** Local and systemic factors causing taste changes

Causes	List of conditions	Mechanism	Clinical features
<b>Local causes</b>			
Local irritants	(Chemical/mechanical/thermal), contact allergy, allergic contact stomatitis, food allergies, food preservatives, additives, flavorings, dental restorations, denture materials, oral care products, mouthwashes	Damage to the taste buds, inflammatory, atrophic, destructive and sclerotic changes in the intra oral mucous membrane and in the taste buds	Hypogeusia, dysgeusia
ENT causes	Mastoiditis and purulent otitis media	Damage to chorda tympani	Taste or sensory intensification or loss of taste and phantoms
Mucosal lesions	Lichen planus, candidiasis	Condition itself may affect taste cells or medications used to treat oral lichen planus may have a secondary affect	Decreased perception of sour taste (5)
<b>Systemic causes</b>			
Medications	Angiotensin-converting enzyme inhibitors, calcium channel antagonists, beta blockers antihyperglycemics, chemotherapeutic agents, antibiotics, anti-inflammatory, anti-epileptics, drugs for endocrine and metabolic disorders, drugs used for gastrointestinal disorders	Chemical interference and the effects on taste receptors during their development and maturity	Hypogeusia, dysgeusia, taste phantoms
Hyposalivation	Connective-tissue disease, autoimmune disorders, iatrogenic conditions (such as drug-induced or associated with radiation therapy), anxiety or stress, radiation therapy, xerostomia, medications	Reduction in saliva causes lack of solvent for the dissolution of food substances and also lack of protective effect of saliva on the taste cells	Hypogeusia, dysgeusia and taste phantoms
Cancer	Head and neck cancer, cancer treatment (surgery, radiation therapy, chemotherapy)	Damage to taste buds, nerves supplying taste, salivary glands and mucosal epithelium due to condition or sequelae of side effects of treatment	Hypogeusia, dysgeusia, taste phantoms
Deficiencies	Iron, vitamin B12, folate, zinc, vitamin B complex (B1, B2, B6), E	Atrophic glossitis. A study has also suggested that Vitamin E may play a role in development and growth of stem cells in olfactory epithelium and taste buds	Threshold for sour is slightly higher in patients with iron and zinc deficiency
Infections (bacterial, fungal, viral)	Bell's palsy HIV candidiasis herpes simplex, herpes zoster, COVID, dengue, leprosy, Ramsey hunt, influenza, common cold hepatitis C (46-54)	Damage of the intra oral mucosal epithelium and secondary damage to the olfactory epithelium	Hypogeusia, dysgeusia, taste phantoms
Endocrine disorders	Diabetes, thyroid disease	Inhibitory effect on development and maturation of fungiform papillae	Hypogeusia, dysgeusia
Autoimmune disorders	Sjogren's syndrome	Hyposalivation and effects on taste buds	Hypogeusia, dysgeusia, taste phantoms
Others	Chronic kidney disease, transplant, gastro esophageal reflux disease (55,56)	Deficiencies of water-soluble vitamins B, C due to dialysate and possible dietary restrictions	Hypogeusia, dysgeusia, taste phantoms
Trauma	Middle ear surgery, tonsillectomy, third molar surgery	Damage to nerves supplying taste	Hypogeusia, dysgeusia, taste phantoms
Damage in taste pathway	Tegmentum lesion in midbrain or pons, lesions in thalamus, pontine hemorrhage	Damage to nerves supplying taste	Hypogeusia, dysgeusia, taste phantoms
Psychological	Anxiety, perceived stress, state and trait anxiety, depression subjective dryness (3)	Psychological causes	Hypogeusia, dysgeusia, taste phantoms

pathway (76) and GABA receptors have been reported in the CNS/PNS. Patients with BMS have reported good efficacy with GABA agonists such as clonazepam (38). Since, inhibition of taste may produce oral pain/burning it is conceivable that use of GABA agonists may counter the inhibitory effect of taste loss (67) or it may reduce burning sensation to improve taste. A recent study has shown that reduction of oral pain and burning may improve taste (38).

### **Taste changes in local and systemic pathologies**

Mechanical, thermal and chemical irritants may damage the taste buds and thus produce taste changes or taste phantoms. Allergic contact stomatitis, food allergies, additives, preservatives, food flavorings, dental restorations, denture materials, oral care products including mouthwashes may induce changes in taste. A recent animal study on the role of chemicals in dental materials on taste changes has shown inflammatory, atrophic, destructive, sclerotic changes in the intra oral mucous membrane and in the taste buds (77). Mouthwashes containing chlorhexidine gluconate may induce hypogeusia to salt, bitter tastes and dysgeusia; which may last for few weeks even after discontinuation of the mouthwash (78).

Pathologies in the Ear Nose Throat (ENT) such as mastoiditis, purulent otitis media, upper respiratory infections have been reported to induce changes in taste. In these cases, perception of PROP bitterness is also reduced (79). Approximately 31.2% patients with allergic rhinitis report taste disorders (80). Middle ear infections may cause physical damage to chorda tympani and result in taste or sensory intensification or loss of taste and phantoms (79). Taste changes have been reported in mucosal lesions such as lichen planus. The prevalence of taste disorders in oral lichen planus is estimated to be approximately 0.5% (81). However, majority of the patients fail to notice subjective taste loss. Objective quantification of taste loss by Suter and colleagues has suggested that the prevalence may be much higher. Objectively, patients with oral lichen planus may have a decreased perception of sour taste (5). The study reported that the condition itself may affect taste cells or the medications used to treat oral lichen planus may have a secondary effect on taste.

It is estimated that 9–22% of taste disorders may be secondary to drugs (6). A study in Netherlands on approximately 1,645 drugs suggested that 20% of patients may experience dysgeusia and hypogeusia (82). Drugs that have been reported to cause taste changes include beta

blockers, ACE inhibitors, calcium channel antagonists, antimicrobials, anti-inflammatory, anti convulsants, endocrine and metabolic drugs, chemotherapeutic agents and drugs for gastrointestinal disorders (83–89). Several medications may induce taste disturbances through chemical interference and their effects on taste receptors during their development and maturity and subsequently induce oral pain through CNS mechanisms such as disruption of tonic inhibitory processes (90). Additional mechanisms may include interaction with taste buds (due to local application, absorption into saliva or chronic use), distortion of taste or olfactory signals, qualitative or quantitative effects of drugs on saliva, drug interactions due to polypharmacy, individual predisposition, dose, duration of drugs (82).

Saliva acts as a solvent for the dissolution of food substances and also protects the taste cells. Various connective tissue disease, autoimmune disorders like Sjogren's, salivary gland disorders, iatrogenic conditions (such as drug-induced or associated with radiation therapy), anxiety or stress may induce hyposalivation or xerostomia and thus affect taste. Trait anxiety, state anxiety, depression, stress, and female gender have a significant association with subjective oral dryness (3).

Patients with cancer frequently report taste disorders. This may be a consequence of the pathology (example: tongue cancer) or as a result of treatment (surgery, radiation therapy and chemotherapy). Surgery for tumors in the head and neck especially the tongue may damage the nerves supplying taste. Radiation therapy and chemotherapeutic agents may damage the taste buds, nerves and mucosal epithelium. Radiation therapy for head and neck cancer may damage the salivary glands and induce xerostomia or hyposalivation which in turn may affect taste. Xerostomia/hyposalivation may cause candidiasis, lack of solute for dissolution of food molecules, and protective effect on taste buds. Nutritional deficiency (e.g., zinc, vitamin B, iron) secondary to the inability to eat may compound the problem. Following chemotherapy, electro gustatory testing has reported that hypogeusia and hypergeusia may develop in the chorda tympani and greater petrosal nerve area respectively. Hypogeusia for bitter was proportional to number of chemotherapy cycles. Filter paper testing in the same population revealed hypogeusia of the chorda tympani and glossopharyngeal nerve for sweet, salt, sour and greater petrosal nerve for sweet, salt, bitter (91).

Deficiency of iron (anemia), vitamin B12, folate, zinc, vitamin B complex (B1, B2, B6), iron, hemoglobin have been found to have significant association with atrophic

glossitis (92). Threshold for sour is slightly higher in patients with iron and zinc deficiency. A study has also suggested that Vitamin E may play a role in development and growth of stem cells in olfactory epithelium and taste buds (93) and thus have a role in taste disorders. Tobacco and its constituents, and alcohol have a bitter taste. It has been previously suggested that PTC tasters are less likely to smoke/consume alcohol and it may have a protective role in certain populations (94,95).

Bacterial (leprosy), viral (Bell's palsy, HIV, herpes simplex, herpes zoster, COVID-19, dengue, Ramsey hunt, influenza, common cold, Hepatitis C) and fungal infections (candidiasis) are associated with changes in taste (46-54). In several instances, often there is no real-world taste loss even though there is objective loss of taste on anterior 2/3. Taste disturbances in patients with leprosy has been suggested to be secondary to damage to taste buds and nerve fibers carrying taste by leprosy bacillus (96). Hepatitis C patients report higher taste thresholds for sweet and umami (53). Bacterial and viral infection can induce inflammation which activates interferon (IFN) pathways in the taste bud cells and affects mechanisms involved in taste transduction. IFN also plays a role in taste bud cell apoptosis leading to variations in the cell type turnover and proportion of different taste bud cells (97). These mechanisms may result in taste changes.

Endocrine disorders such as hypothyroidism and their effects on taste and burning have been studied. Hypothyroidism may induce dysgeusia for bitter and acid taste and the patients report increased sensitivity to tactile, pain temperature, and tabasco/pepper sauce/spicy food. Hypothyroidism may have inhibitory effect on development and maturation of fungiform papillae. This results in reduced taste perception and disinhibition of the trigeminal system (98,99). Patients with type 2 diabetes are frequently non-tasters to PROP with lesser number of fungiform papillae and also have a low ability to detect sour and bitter (100).

Parkinson's, seizure disorders, ALS multiple sclerosis, and neurodegenerative diseases such as Alzheimer disease, dementia, are associated with changes in taste and smell (101). Taste changes may precede development of these disorders and may be predictive of progression of Alzheimer dementia and cognitive disturbances (101). Patients undergoing dialysis are likely to have deficiencies of water soluble vitamins B, C due to dialysate and possible dietary restrictions (102). These may lead to taste changes. Taste changes have also been reported in chronic kidney disease

(55,56) transplant patients (103), gastro esophageal reflux disease. A case series investigating patients with pontine hemorrhage reported taste deficits in all the patients on the ipsilateral side but all were unaware of the taste loss (104).

### **Taste changes and COVID-19**

Taste loss may be an important predictor symptom in COVID-19. The pooled prevalence of taste changes was estimated to be 41.47% and combined loss of taste and smell was present in 30.04% (105). Taste loss in COVID-19 patients has been proposed to be due to damage of the intra oral mucosal epithelium and secondary to damage to the olfactory epithelium. The SARS-CoV-2 binds and penetrates cells utilizing angiotensin-converting enzyme 2 receptor, which is predominantly expressed on the intra oral epithelial cells (106) and respiratory epithelium. In addition, the virus may induce an inflammatory response and create a barrier to the odor molecules or affect the peripheral and central components of the olfactory pathway. Owing to the contribution of smell to taste perception, COVID-19 patients may exhibit secondary loss of taste (105).

### **Taste changes and nerve injury**

Approximately 31.5% of the patients with upper and middle third facial fractures may present with hypogeusia/ageusia with or without accompanying anosmia/hyposmia (107). Majority of these patients present with the complaints immediately after the trauma and rarely few weeks later. Spontaneous resolution of the complaint is rare and often incomplete even after several years (107). Taste changes are frequently reported after middle ear surgery, tonsillectomy, third molar surgery.

Damage to any component of the taste pathway may result in inability to taste. Taste function is rarely completely lost as it would require damage to multiple nerve, taste receptors and taste pathways. Thus, real world taste loss may be intact even in persons with extensive damage to the tongue or nerves supplying the tongue in spite of clear cut (clear evidence/demonstration) of localized taste loss (108). In a study of anesthesia of the tongue and palate, patients could still perceive taste if they were allowed to swallow (109).

In cases of chorda tympani transection, very few patients report taste loss, few report reduced taste and some patients report taste phantoms. In cases of complete unilateral chorda tympani nerve transection, capsaicin burn was increased on the contralateral side (62) more prominently in supertasters.

In cases of bilateral sectioning of the chorda tympani during middle ear surgery, there was loss of taste on anterior 2/3 but no change in whole mouth taste ratings (110).

Ascending taste pathways are predominantly ipsilateral with few contralateral and bilateral representation (10). However, descending taste pathways (gustatory cortex to NTS in medulla) has ipsilateral and greater contralateral projection and this may be partly responsible for the disinhibition of glossopharyngeal by chorda tympani.

Taste changes may also occur subsequent to iatrogenic injuries during dental procedures such as local anesthesia and third molar extractions. Following third molar extraction especially distoangular and vertical impactions; gustatory and sensory changes (especially to salt and bitter) may be observed (111,112). There are variations in subjective and objective recovery patterns for somatosensory and gustatory sensations. Following lingual nerve injury and bitter and sour are the last to recover (113).

### Assessment

Damage to any component in the taste pathway may induce taste changes. Subjective and objective testing may be accomplished to detect taste loss. However, a majority of the patients fail to perceive the changes. Real world taste loss may be intact even in persons with extensive damage to the tongue or nerves supplying the tongue (114), in spite of clear cut (clear evidence/demonstration) of localized taste loss (108). Localized taste loss occur in specific regions or to particular tastes (115) and may be partial or complete.

Objective assessment may include whole mouth threshold, quality identification, electro gustatory tests, direct scaling tests, spatial test using cotton tipped applicators, filter disc and psychophysical testing.

Additional laboratory and serological testing may be required to diagnose local and systemic factors, autoimmune conditions. QST may be helpful in instances of iatrogenic nerve injury/ trauma. Imaging modalities like MRI may be helpful in cases of suspected lesions in the CNS (e.g., tegmentum lesion in midbrain or pons, lesions in thalamus, pontine hemorrhage, stroke, pontine hemorrhage) causing taste changes.

### QST and BMS

Based on QST profile BMS is further subclassified into BMS with somatosensory changes and BMS without somatosensory changes (116). Electrophysiologic studies

in patient with BMS have demonstrated that these patients exhibit elevated taste threshold, electro gustatory threshold (43,45,73) whole mouth threshold (117) to sweet and sour (118) in the regions that contain highest density of fungiform papillae which are innervated by chord tympani.

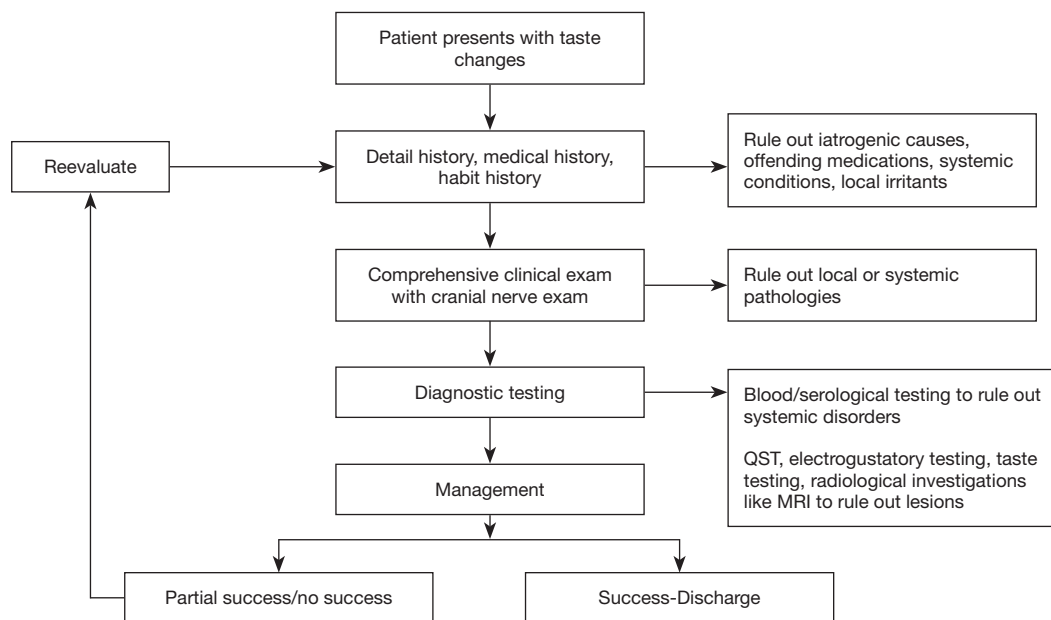
### Management of taste disorders

A detailed history and comprehensive clinical evaluation are essential prior to initiation of treatment. A detailed history may help in identification of precipitating factors such as trauma, allergens, local irritants, medical history, habits (smoking, alcohol). A detailed review of systems should be conducted to identify systemic conditions, offending medications, infections which are likely to induce taste changes. Prodromal symptoms are common in viral infections. A screening cranial nerve examination may identify conditions. Comprehensive extra oral, intra oral, salivary gland, lymph node examination, clinical examination should be conducted to look for intraoral sources such as mucosal lesions, allergens like dental restorations or dental materials in dentures, salivary gland disorders. Diagnosis of contributing local and systemic factors of paramount importance and addressing these is the first step for management of taste disorders. A systematic multidisciplinary approach should be followed to enhance success rate in management of taste disorders. This includes correction of micronutrient deficiencies, identifying and removing medications, allergens that are known to interfere with taste (7), identifying and treating underlying systemic disorders. Several conditions are self-limiting and resolve following acute phase of the disease, e.g., COVID-19, Bells palsy. In case of viral conditions such as COVID-19 it may be part of the presentation and recovery of taste generally occurs within 3 weeks of recovery (106). Treatment with thyroid hormones largely reversed both the taste and smell defects. In one case, taste and smell abnormalities were completely corrected after 16 days of treatment with thyroxine (119).

A systematic review on prophylaxis and management of dysgeusia in cancer patients receiving treatment has suggested that zinc sulfate and amifostine have a limited value in prevention and prophylaxis of taste changes (120). Nutritional counseling may be of benefit in these cases.

Management of oral pain in BMS patients with the use of clonazepam, tri cyclic antidepressants, gabapentinoids, alpha lipoic acid, zinc supplements may help in subjective improvement of taste disorders (38).





**Figure 1** A paradigm for the evaluation and management of patients with taste alterations.

Management of taste disturbances secondary to trauma or iatrogenic injury depends on the degree of injury. QST may be of value in diagnosing whether it is purely inflammatory pain or there is actual nerve damage. Iatrogenic nerve injuries accompanied by pure inflammatory neuritis as diagnosed with QST may be treated with steroids in early stages (121). Instances of nerve transection secondary to third molar surgery, middle ear surgeries may benefit from micro neurosurgical repair. There is significant somatosensory and chemosensory/gustatory recovery following micro neurosurgical repair although there is variation in subjective and objective results (122,123). Chorda tympani nerve transections in ENT surgeries treated with surgical repair has led to the regeneration of papilla (124) and improvement in taste (Figure 1).

Effective management is still elusive in idiopathic hypogeusia and dysgeusia. Nutritional counseling may be of benefit. A recent systematic review has concluded that there is very low evidence for use of zinc/to treat taste disturbances in idiopathic taste disorders/zinc deficiencies/chronic renal failure very low evidence for acupuncture in idiopathic dysgeusia and hypogeusia (125,126). Pilocarpine, alpha lipoic acid, transcranial magnetic stimulation, ginkgo biloba has been suggested. However well controlled studies are lacking to allow definitive conclusion (125). Intranasal theophylline methyl propyl paraben has shown promising results in a pilot study with hypogeusia (127).

Well conducted RCT's are required in future to enable us to draw definitive conclusions.

## Conclusions

Taste disorders may be the result of normal physiological changes or may be secondary to pathology. A variety of local, systemic factors, BMS and chorda tympani nerve injury may induce taste changes. A detailed clinical history, medical history, review of systems and comprehensive clinical examination are vital/paramount for identification of underlying pathophysiological mechanisms. Multidisciplinary management enhances the rates of success in treatment.

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## Footnote

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