# 5 Olfaction and Taste

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**Abstract**
Smell and taste loss are becoming increasingly recognized as important conditions with high prevalence and significant impact on the quality of life. Olfactory dysfunction is the only sensory impairment that is associated with an increased risk in mortality. It is also known to be associated with decreased quality of life, social anxiety, and depression. Both olfaction and taste gradually decline with age and can be associated with a wide spectrum of disease. However, these chemosensory impairments are not well understood, and their treatment options remain limited. This chapter highlights the spectrum of olfactory and taste disturbances, their etiologies, workups, and treatment options.

*Keywords*: smell, taste, olfaction, olfactory loss, smell loss, smell disorders, anosmia, hyposmia, parosmia

**Pearls**

- Olfactory loss and taste dysfunction are common disorders that are often underdiagnosed and lead to decreased quality of life, depression, and increased mortality.
- Olfaction disorders can be divided into conductive and sensorineural etiologies, with the most common being post-upper respiratory infection, chronic rhinosinusitis, head trauma, toxins/drugs, congenital, and idiopathic.
- Olfactory dysfunction can herald early neurodegenerative disease, nasal masses, or sinonasal disease; thus, workup should include a complete head and neck examination as well as objective smell and taste testing.
- While a variety of investigative therapies and vitamins have been proposed, olfactory training, steroid irrigation, omega-3, and now PRP injections, are the only beneficial therapies for olfactory loss with evidence based on randomized controlled trials.
- Similarly, there is a paucity of evidence for the efficacy of treatments for taste disturbances although multiple therapeutics such as zinc, alpha lipoic acid, and acupuncture have been proposed.

## 5.1 Introduction

Olfactory loss and taste dysfunction are becoming increasingly recognized as important conditions with high prevalence and significant impact on the quality of life. Olfactory dysfunction is the only sensory impairment that is associated with an increased risk in mortality.[1] It is also known to be associated with decreased quality of life, social anxiety, and depression.[2] Both olfaction and taste gradually decline with age and can be associated with a wide spectrum of disease. However, these chemosensory impairments are not well understood, and their treatment options remain limited. This chapter highlights the spectrum of olfactory and taste disturbances, their etiologies, workups, and treatment options.

## 5.2 Olfaction

### 5.2.1 Epidemiology and Anatomy

#### Epidemiology

Through the 2011–2012 National Health and Nutrition Examination Survey (NHANES), over 10% of the adult respondents self-reported olfactory dysfunction in the last 12 months, and of this population, 50% reported their olfactory dysfunction was persistent.[3] The prevalence increased with age but without any gender predilection. A more recent assessment of the updated NHANES database demonstrated that age, race, gender, education, exposure to vapors, urinary levels of manganese, 2-thioxothiazolidine-4-carboxylic acid, 2-aminothiazoline-4-carboxylic acid, 2,4 dichlorophenol, and serum lead levels are all implicated in smell disturbance.[4] More objective assessments of olfactory dysfunction have been performed in a variety of target populations.[5] In Germany, Vennemann et al found impaired olfaction in 21.6% of randomly screened adults with 3.6% being anosmic.[6] In the United States, the 2002 Epidemiology of Hearing Loss Study found olfactory dysfunction in 24.5% of the older adults (aged 53–97 years) screened versus 9.5% self-reported cases, suggesting a poor ability to self-assess for olfactory loss.[7] The COVID-19 (coronavirus-19) pandemic added to the already high prevalence of olfactory dysfunction. In the United States alone, as of November 2022, 66 million Americans reported they had experienced smell and taste loss from a COVID-19 infection, with over 15% of those individuals having persistent smell dysfunction beyond 6 months. Two years in, the pandemic added 9 million more Americans with long-term smell loss, and 3 million more with smell distortion, with the numbers continuing to grow.[8]

#### Anatomy

The olfactory cleft is a narrow space in the superior nasal cavity bordered medially by the superior septum and laterally by the middle and superior turbinates.[9] Within this space lies the pseudostratified columnar epithelium, which contains the olfactory mucosa, and the underlying lamina propria, separated by a basal lamella. The cell types of the mucosa include the olfactory receptor neurons (ORNs), the sustentacular or support cells, and the basal cells (▶ Fig. 5.1).

The ORNs are bipolar receptor cells with ciliated dendrites residing in the mucus-covered epithelial layers and axons extending intracranially through the cribriform plate to synapse at the olfactory bulb.[10] These cells serve as both a receptor cell and a first-order neuron, making them particularly vulnerable to neurotropic viral agents.[11] The sustentacular or supporting cells insulate the ORNs and help degrade odors and transport molecules across the epithelium. The basal cells act as stem cells that

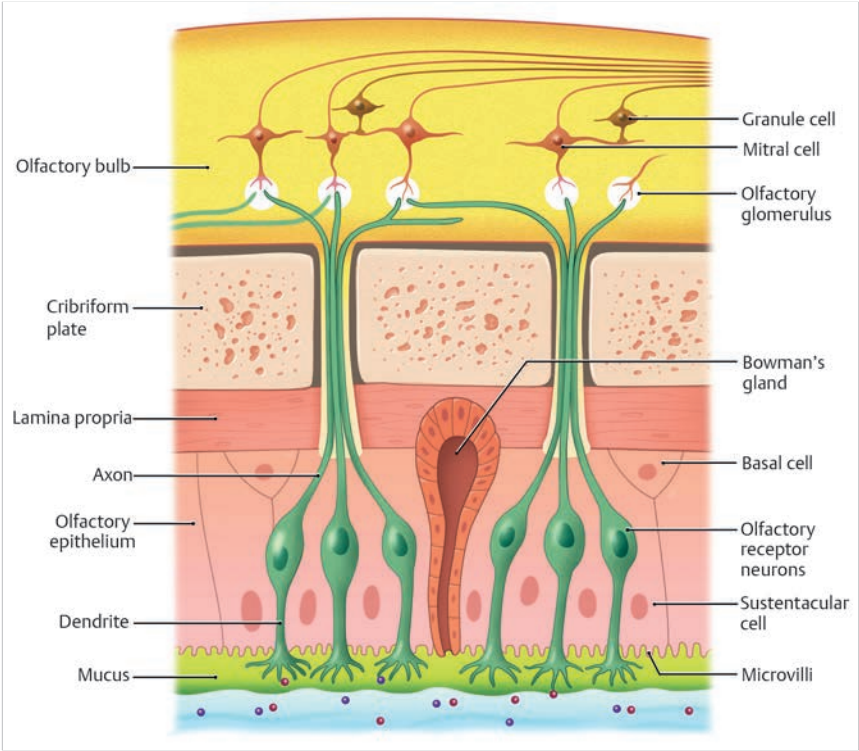


**Fig. 5.1** Illustration of the olfactory epithelium and the olfactory bulb.

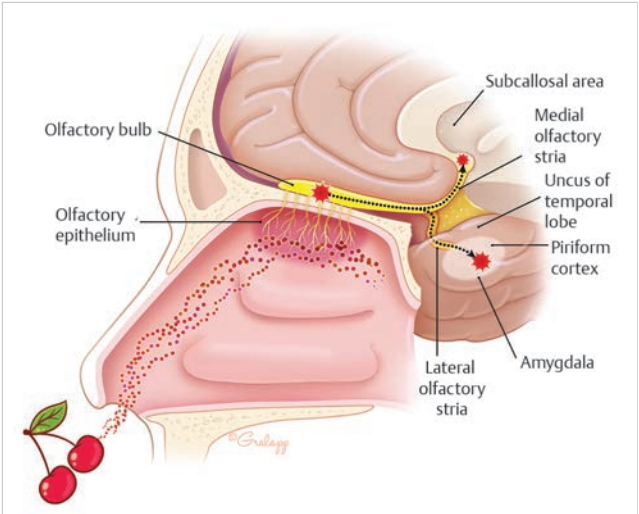


**Fig. 5.2** Illustration of the synaptic pathway from the olfactory epithelium to higher order processing centers in the cortex.

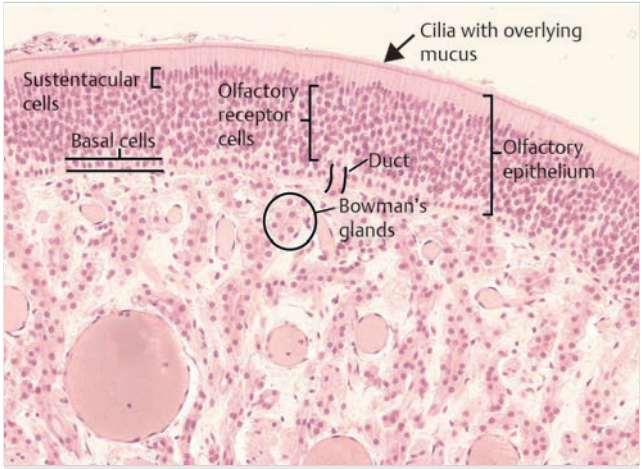


**Fig. 5.3** Histology of the olfactory epithelium at 203x magnification. (Copyright of the University of Iowa's Department of Pathology Virtual Slidebox.)

promote olfactory epithelium regeneration. After injury, the basal cells can divide and differentiate into all cell types within the olfactory system, including olfactory neurons. There is some evidence that this regenerative ability is promoted by increased exposure to odors.[12,13] However, their ability to regenerate decreases with age. Within the lamina propria are Bowman's glands, specialized glands that produce mucus that in turn helps protect the ORN and allows for binding with odorant molecules.

## Olfaction Signal Transduction

The initial step in olfactory transduction is the movement of odorants from the air phase of the nasal cavity into the aqueous phase of the olfactory mucus. Each ORN contains one olfactory receptor, but most odorants can bind to and stimulate multiple olfactory receptors. Conversely, one receptor can also bind to multiple odorants. This combination allows for thousands of odors to be identified by humans. When specific olfactory receptors are activated, their axons synapse at the olfactory bulb located in the anterior cranial fossa at the base of the frontal lobe. In the glomeruli of the olfactory bulb, second-order neurons (mitral and tufted cells) lie and their axons travel via the lateral olfactory tract to synapse at the primary olfactory cortex (▶ Fig. 5.2 and ▶ Fig. 5.3).[10]

**Table 5.1** Common causes of olfactory dysfunction

| | |
|---|---|
| Conductive | • Rhinosinusitis<br>• Nasal polyposis<br>• Nasal cavity tumor |
| Sensorineural | • Post-URI/viral<br>• Trauma and head injury<br>• Congenital<br>• Toxins<br>• Medications<br>• Aging<br>• Neurodegenerative disorders:<br>◦ Alzheimer's disease<br>◦ Parkinson's disease |

Abbreviation: URI, upper respiratory infection.

## 5.3 Clinical Olfactory Disorders

Olfactory disorders can be classified as either the loss of ability to detect odorants (quantitative disorders) or the distortion of odors (qualitative disorders); they are classified as "-osmias." Anosmia refers to the complete loss of smell, whereas hyposmia is the decreased ability to smell. Dysosmia refers to the distortion of the quality of odors and can include parosmia (sensation that an odorant is different from its typical smell), phantosmia (perception of an odor in the absence of a source), and olfactory agnosia (inability to recognize odorants).[9] These qualitative olfactory disorders can affect a patient's quality of life to a greater extent.

Olfaction disorders can be divided into conductive and sensorineural, and include both peripheral and central causes (▶ Table 5.1). The most common etiologies of olfactory disorders include post-upper respiratory infection (post-URI; 26–36%); chronic rhinosinusitis (CRS; 15–21%); head trauma (17–18%); and toxins/drugs, congenital, and idiopathic (18–22%).[14] There are hundreds of causes of olfactory dysfunction and in this chapter we will only address the most common etiologies.

### 5.3.1 Conductive Olfactory Disorders

#### Chronic Rhinosinusitis and Allergic Rhinitis

Olfactory dysfunction has a high prevalence in CRS patients, between 30 and 78% of that population, and is associated with decreased quality of life.[15] Nasal polyposis is the most frequently associated comorbidity in patients with CRS and higher Lund–Mackay computed tomography (CT) scores are associated with worsened smelling ability.[15] Olfactory dysfunction as a result of CRS is likely both a conductive and a sensorineural disorder due to the physical blockage of odorants to the olfactory cleft as well as a chronic inflammatory state that is damaging to the nasal epithelium containing bipolar neurons. In addition, chronic inflammation leads to decreased stimulation of the olfactory bulb, which results in a subsequent loss in volume.[16] The sensorineural damage may explain why restoring olfactory function after endoscopic sinus surgery (ESS) can be difficult in CRS patients even after the physical obstruction has been removed. In CRS patients with nasal polyposis, however, surgical treatment can increase olfactory bulb volume and decrease odor thresholds.[17] Studies have also reported a 20 to 40% prevalence of olfactory dysfunction in patients with allergic rhinitis (AR), which is higher with increased duration of AR and perennial symptoms.[18]

#### Sinonasal Masses

Sinonasal tumors including hemangiomas, esthesioneuroblastomas, inverted papillomas, other benign tumors, and sinonasal malignancies may cause a conductive olfactory loss and may be associated with epistaxis, headache, or airflow obstruction. Intracranial tumors or lesions including frontal lobe gliomas and olfactory groove meningiomas may also present with headaches and smell loss as well as other neurological deficits.

#### Trauma

Olfaction dysfunction is common after head trauma affecting approximately 20 to 30% of patients, depending on the mechanism of injury.[19] Trauma causes conductive olfactory dysfunction with altered cartilaginous and bony anatomy from nasal fractures and hematomas as well as scarring after mucosal damage. These same injuries may cause sensorineural deficits from direct injury or more oftentimes shearing of the olfactory nerve fibers at the cribriform plate.[20] Injury at the level of the cortex more often causes impaired odorant recognition rather than detection.[21] Recovery is often related to the extent of the head trauma, but spontaneous recovery may occur in about a third of patients, up to a year or more after injury.[19,22,23]

#### Iatrogenic

Olfaction loss after endoscopic sinus and skull base surgery, although fortunately uncommon, is a potential postoperative complication and must be addressed in the informed consent. In an analysis of malpractice litigations involving olfactory dysfunction, otolaryngologists were the most frequently named defendants, for procedures of which most were rhinologic.[24] These procedures included routine septoplasties or turbinate reductions as well as more involved frontal sinus and skull base surgeries. Although evidence is limited and conflicting, most studies suggest that patients can have temporary olfactory dysfunction following skull base surgery regardless of approach, and some may be at risk of more permanent problems.[25,26,27] Aside from surgery, it is important to remember that patients who undergo radiation therapy or total laryngectomy for head and neck cancers almost always have a degree of iatrogenic olfactory loss. Hyposmia was reported in 100% of patients postlaryngectomy, and hypogeusia in over half.[28]

### 5.3.2 Sensorineural Olfactory Disorders

#### Upper Respiratory Infection

Upper respiratory infections, usually viral, are the most common causes of permanent hyposmia and anosmia.[10] A good

number of unknown causes of anosmia may be viral as these infections can be mild or asymptomatic. The pathogenesis of the sensory olfactory loss following an upper respiratory infection is not well known but thought to be related to damage to the neuroepithelium either directly or through inflammation. Biopsy studies from post-viral insult of the olfactory epithelium reveal increased scar degeneration and decreased cilia, suggesting direct injury to the olfactory epithelium.[29] There is also a decrease in olfactory bulb volume.[16] Patients present with more parosmia from this etiology compared with other causes of olfactory dysfunction. In patients with postinfectious olfactory loss, 35 to 67% see at least partial spontaneous recovery usually within 2 to 3 years postinfection.[16,23,30] A large retrospective review suggested that of patients who suffered from postinfectious loss, those with initial greater olfactory dysfunction and younger in age were more likely to show greater improvement in olfaction over time.[31]

### Age

Increasing age is well known to be associated with olfactory loss. Under the age of 65 years, about 2% of the population has chronic hyposmia or anosmia, but between 65 and 80 years, about half the population develops smell dysfunction and over the age of 80 years, nearly 75% of the population has problems with olfaction. The pathophysiology may be a result of a combination of the ossification and closure of the foramina of the cribriform plate, the possible development of neurodegenerative diseases at that age, and repeated assaults over a lifetime to the superficially located olfactory receptor cells.[32]

## 5.3.3 Neurodegenerative Disorders

In patients with Alzheimer's disease (AD) and Parkinson's disease (PD), approximately 90% exhibit olfactory dysfunction in the early stages of the diseases. Olfactory loss may, in fact, be the first clinical sign of these neurodegenerative diseases, preceding signs of dementia in AD or motor symptoms in PD by several years.[33,34] In addition to poor odor identification, unawareness of smell impairment is also associated with AD; patients do not usually present with complaints of smell or flavor dysfunction. Unfortunately, the olfactory dysfunction does not seem to improve with treatment of anti-PD medications.

Patients with otherwise unexplained olfactory dysfunction and the presence of the apolipoprotein E (apo E) allele had a 4.9 times higher risk of developing cognitive decline compared to those who were normosmics without the allele.[35] Among first-degree family members of those with PD, those who developed olfactory dysfunction were at an increased risk of developing PD within 2 years and similar olfactory deficits were found in family members of AD patients.[36,37]

Other neurologic diseases characterized by olfactory deficits include Huntington's disease, neuro-HIV, and multiple sclerosis, among others.

### Congenital

Congenital anosmia accounts for approximately 1 to 3% of all anosmia cases and can be found in either isolation (majority of the cases) or as part of a syndrome. These patients often present with an inability to smell their entire life but are not diagnosed until preteen years by family members, with it often being a diagnosis of exclusion. Most of the reported congenital anosmia cases are sporadic, while the familial cases are via all modes of inheritance. For some of the syndromic cases, multiple causative genes have been identified.

Of the congenital anosmias associated with various syndromes, Kallmann's syndrome is the best described and consists of isolated hypogonadotropic hypogonadism and anosmia. These patients typically lack olfactory bulbs as well as the gonadotropin-releasing hormone (GnRH). The defects are due to a lack of migration of GnRH-releasing cells from the olfactory placode to the hypothalamus and a lack of migration of the olfactory neurons to the olfactory bulb and hypothalamus.[38] At least six causative genes have been associated with Kallmann's syndrome with all types of mutations.[39] Anosmia is also associated with holoprosencephaly, anterior neuropore anomalies, Turner's syndrome, retinal dystrophies, and a congenital insensitivity to pain.

Depending on the cause of anosmia, magnetic resonance imaging (MRI) findings may reveal aplasia or hypoplasia of the olfactory bulb, or associated encephalocele or abnormality in the frontal lobe (▶ Fig. 5.4).

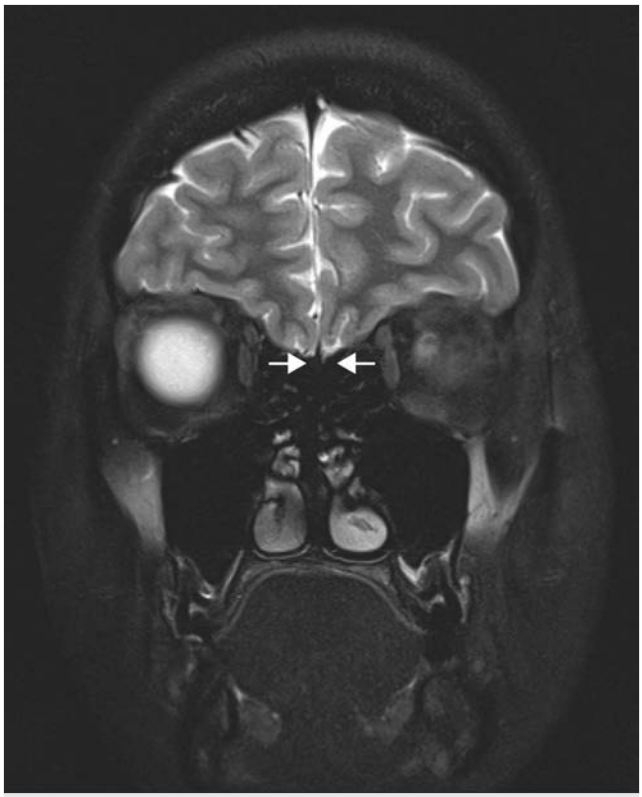

**Fig. 5.4** Lack of olfactory bulbs or tracts (*arrows*) in a 21-year-old woman with congenital anosmia on a T2-weighted high-resolution coronal magnetic resonance image.

### Drugs and Toxins

The number of patients with olfactory dysfunction attributed to toxin exposure is relatively low (2%), but a large number of toxins are associated with olfactory loss.[40] Airborne toxins, such as herbicides and pesticides, as well as heavy metals, such as cadmium, chromium, nickel, and manganese, have all been associated with olfactory loss, particularly with chronic exposure.[11] The olfactory neurons are in direct contact with the nasal environment and are at risk of toxin and viral exposure. Supporting cells and Bowman's glands contain cytochrome P450 enzymes, which help detoxify inhaled or systemic toxins. If the basal cells are spared, the olfactory neurons may regenerate after an acute toxic injury, but repeated injury and increasing age decrease regenerative olfactory potential.

Tobacco smoke exposure is associated with hyposmia in active smokers.[41] Rat studies found increased olfactory receptor neuron apoptosis with tobacco smoke exposure.[42] A meta-analysis concluded that current smoking, but not former smoking, is associated with increased risk of olfactory dysfunction, suggesting that the effects of smoking may be reversible.[43]

## 5.4 Diagnostic Workup

The approach to a patient with an olfaction problem should be thorough and systematic given the extensive etiology of olfactory disorders.

### 5.4.1 History and Physical

A thorough patient history taking should include the duration and degree of olfactory loss, inciting factors, head injuries, environmental exposures or toxins, sinonasal symptoms, endocrine or neurologic problems, past surgical history, prior cancer treatment even if not for the head and neck region, tobacco usage, medications, and a family history of olfactory loss or neurodegenerative problems. A physical examination should incorporate an otolaryngologic as well as a neurologic examination. Emphasis is to be placed on the nasal airway evaluation, including evaluation of the middle meatus, superior meatus, and olfactory cleft for edema, masses, scarring, or polyps.

### Olfactory Testing

The most common olfactory test used in the United States is the University of Pennsylvania Smell Identification Test (UPSIT), a well-validated, self-administered examination that includes 40 "scratch and sniff" odorants used screen for olfactory dysfunction. Scores are evaluated based on a 4,000 person normalized scale and the patient is classified as either having normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia, or probable malingering.[44] The Cross-Cultural Smell Identification Test (CC-SIT), also known as the Brief Smell Identification Test (B-SIT), is a 12-item version of the UPSIT, which is useful for rapid screening and ruling out a smell problem, but is not as sensitive as the full version and is not granular enough to track changes in an individual over time or after treatment.[45]

The Sniffin' Sticks test is the most common olfactory test used in Europe to assess orthonasal olfactory function as odor-dispensing sticks are presented in front of the patient's nose; the patient is evaluated on odor threshold, discrimination, and identification (TDI) and compared to normative data.[46]

There are several other tests that have been utilized for both clinical and research purposes, including the Barcelona Smell Test-24 (BAST-24), the Connecticut Chemosensory Clinical Research Center Olfactory Test, and the T&T olfactometry test.[47,48,49] The most important factor in deciding which test to utilize is verifying that it has been validated in the literature and acceptance has been demonstrated via widespread use.

### Imaging

Workup of olfactory dysfunction also includes radiographic imaging. A CT scan of the paranasal sinuses may help diagnose CRS, tumors, and any unusual anatomy. Volumetric measurement of olfactory cleft opacification on CT is associated with olfactory dysfunction in patients with CRS.[50] MRI, however, is the preferred imaging modality to evaluate for the olfactory bulb, tract, and cleft (▶ Fig. 5.5). The olfactory bulb volume and sulcus depth are smaller when olfactory dysfunction is more pronounced, and tumors are more readily seen using this mode of imaging.

## 5.5 Treatment

### 5.5.1 Patient Counseling

For patients with hyposmia and anosmia, it is important to counsel them about their awareness of hazardous exposures

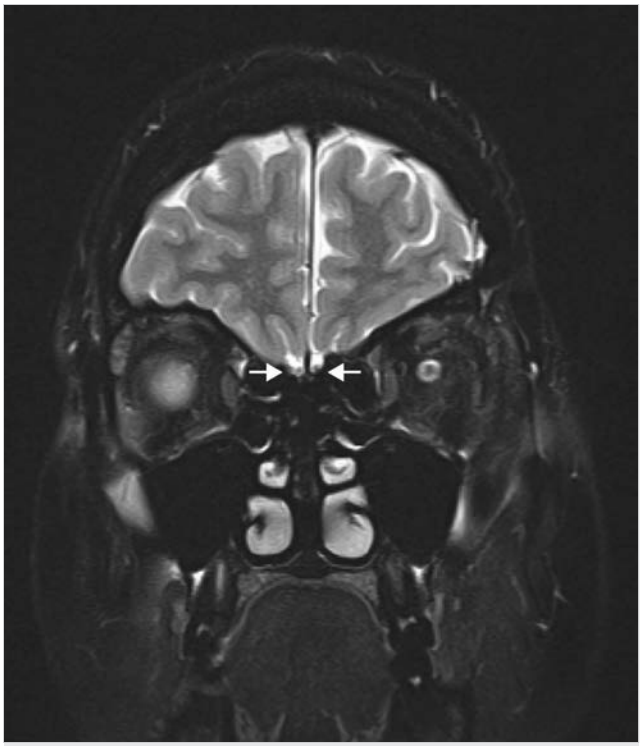

**Fig. 5.5** High-resolution T2-weighted magnetic resonance image in the coronal plane demonstrates the olfactory bulb/tracts (*arrows*) in the anterior cranial fossa inferior to the frontal lobe.

without a sense of smell. This includes fire safety and gas leakage and the installation of smoke detectors and carbon monoxide detectors at home and work. Patients must also be cautious of spoiled foods and pay attention to labels for expiration dates. As mentioned previously, hyposmia may be a precursor of dementia, so signs of cognitive decline must be looked for.

Additionally, as significant loss of smell impairs the ability to taste anything beyond the basic characteristics of sweet, salty, sour, bitter, and umami, the substantial social and emotional impact of never being able to taste and enjoy the flavor of food and drink often becomes overwhelming to patients, leading to social isolation and depression.[51] Counseling to acknowledge and validate these feelings is also important in treating this patient population, and awareness that they are not alone in feeling these things can go a long way toward helping them cope.

## 5.5.2 Olfactory Training

Olfactory training has been shown to improve the TDI and UPSIT scores in patients with olfactory dysfunction as shown in two meta-analyses and many randomized controlled trials.[52,53,54] In both meta-analyses, there was an improvement in the subcategories of discrimination and identification and less so in olfactory threshold. In the randomized controlled trial, olfactory training similarly improved olfaction identification using UPSIT, with prior evidence showing good correlation with discrimination. This is the best evidence we have for appropriate therapy for olfactory dysfunction at this time. Olfactory training is the repeated exposure to different odors with the goal of promoting regeneration of progenitor cells in the olfactory epithelium. Patients select odors from different odorant categories such as floral, fruity, aromatic, and resinous, and work on smelling these scents twice a day for 12 to 56 weeks.[55] Hummel et al first wrote about olfactory training using a 12-week course of four odors (rose, eucalyptus, clove, and lemon) and demonstrated improved olfactory sensitivity in patients with olfactory dysfunction from different etiologies.[56] A randomized controlled study showed that training with odors at higher concentrations resulted in greater improvement, suggesting that it is not the act of sniffing alone that can be attributed to the olfaction response.[57] Also, not surprisingly, an olfactory loss of less than 12 months had a significantly higher rate of improvement.[58] Furthermore, longer duration of olfaction training has been prospectively studied using up to 24 or 56 weeks instead of 12 to show greater improvement after a postinfectious olfactory loss.[58,59] The clinical improvements on olfactory training are also visible on functional MRI (fMRI), which shows more organized neuronal connectivity from the olfactory bulb to the cortex, as well as increased olfactory bulb size.[60,61]

## 5.5.3 Topical and Systemic Steroids

Steroids play a role in the treatment of inflammation and olfactory loss. Cells in the olfactory mucosa contain sodium, potassium-adenosine triphosphate (Na, K-ATPase) that are regulated by corticosteroids.[62] Increased proinflammatory cytokines have also been found in patients with hyposmia including tumor necrosis factor-alpha and interleukin 4 and 6.[63,64,65] These findings may explain why systemic steroids can improve olfactory function in CRS-related olfactory loss. Topical steroid sprays can also be efficacious in CRS-related smell loss, although to a lesser degree than oral steroids, without the many adverse side effects associated with long-term systemic steroid use. The distribution of topical steroids is important to note as the olfactory recess is difficult to reach with a nasal spray alone, although tilting the head upside-down may help. Steroid rinses with a bottle system have been shown to improve efficacy compared to those with a nasal spray.[66] In AR-driven olfactory loss, treatment may also include topical antihistamine and cromolyn sprays as well as overall allergy management. AR patients with olfactory dysfunction were shown to have improved olfactory outcomes at 1 and 3 months after treatment with a combination of azelastine and fluticasone nasal sprays.[67]

There are some studies that support the use of steroids in olfactory dysfunction without CRS, but until recently, the data remained equivocal. In two studies, URI-induced hyposmic patients treated with prednisolone showed improvement in their odor TDI scores compared to controls.[68,69] However, in trauma-induced olfactory dysfunction, there was no improvement in olfactory threshold detection following prednisolone treatment.[70] In a recently completed randomized controlled trial, it was shown that budesonide irrigations combined with olfactory training were significantly more effective in bringing back olfactory ability than olfactory training alone.[71] This confirms the importance of being able to effectively deliver medication exactly where it is needed within the nasal and sinus cavity in patients with olfactory loss, and how topical therapy can deliver highly potent medications without the side effects of systemic absorption.

## 5.5.4 Endoscopic Sinus Surgery

The role of ESS for CRS has been well studied and validated by multiple prospective studies. Particularly in CRS patients with nasal polyposis, ESS is an effective treatment as shown in a recent systematic review by Kohli et al.[50] However, there still remains a lack of consensus on the extent of surgical intervention required to achieve improvement in olfaction.[72] Patients should undergo counseling regarding the unpredictable nature of possible improvement in olfaction after surgery. Furthermore, the utility of surgery in treating olfactory dysfunction due to causes other than CRS is not established and not recommended.

In patients with phantosmia who report unpleasant and often distressful odors when they are not present, surgical treatment with the removal of the olfactory epithelium has been attempted.[73] The idea behind this treatment is that phantosmia may be a peripheral problem in the olfactory mucosa or axons or a central phenomenon with a peripheral stimulus.[74] Leopold et al described a case series of eight patients who were treated with transnasal and transethmoidal endoscopic resection of their olfactory mucosa along the cribriform plate with sharp excision of the olfactory fila and subsequent coverage with a mucoperiosteal graft.[74] The authors reported resolution of phantosmia in seven out of eight patients. This procedure, however, poses the risk of complete loss of smell, and has not yet been validated in controlled trials due to the rarity of the disorder and rare need for this more drastic intervention.

## 5.5.5 Investigational Treatments for Olfactory Dysfunction

It should be emphasized that at this time, the only beneficial therapy with level 1 evidence (systematic review of multiple randomized controlled trials) for treatment of olfactory dysfunction is olfaction training. The therapies outlined above and below with benefit in non–CRS-related olfactory less, shown in randomized controlled trials, are high-volume steroid irrigation, omega-3, and platelet-rich plasma (PRP) injections into the olfactory cleft. There are currently no medications currently labeled for the treatment of olfactory loss. There have been a number of other investigational drugs and vitamins proposed to treat olfactory dysfunction, and some of these are also presented in this chapter. However, except for those listed directly above, no others have been evaluated using randomized trials, and many studies lacked even a simple control group.

## 5.5.6 Omega-3

Omega-3 has been shown to improve nerve regeneration.[75] A multi-institutional randomized controlled trial was run on patients undergoing endoscopic skull base surgery to assess how many of these patients were suffering from long-term smell dysfunction when quantitatively tested, as well as evaluating the potential benefit of high-dose omega-3.[27] In this study, almost a quarter of patients still had persistent smell dysfunction 6 months out from surgery, but the patients in the omega-3 group had significantly less, with only 4.3% having persistent loss.

This same protocol was replicated in a trial assessing the efficacy of omega-3 in post-viral olfactory loss, and improvements were also seen in these patients.[76]

## 5.5.7 Platelet-Rich Plasma

PRP has been utilized for many years in several different medical fields to help with wound healing and tissue regeneration, commonly used in the fields of orthopaedics and aesthetics, but with many different surgical specialties beginning to investigate utility.

A pilot study on a small group of patients was run to first establish safety and feasibility of PRP injections into the olfactory cleft for potential olfactory nerve regeneration and smelling ability.[77] This did demonstrate safety and patient tolerability.

This was then followed by a randomized controlled trial of 35 patients, specifically for COVID-19-induced smell loss, which compared PRP submucosal injections into the olfactory cleft versus sham saline injections. The patients in the PRP arm had a greater than 12 times odds of smell improvement compared to the sham injection group, with 57% versus 8.3% obtaining meaningful improvement.[78]

These results have been supported by nonrandomized and uncontrolled studies on smell loss as well.[79,80]

## 5.5.8 Theophylline

Cyclic adenosine monophosphate (cAMP) levels and cyclic guanosine monophosphate (cGMP) are important second messengers in olfaction and their levels are lower in the saliva and nasal mucus of patients with loss of smell and taste compared to healthy controls.[81,82] One group of researchers have suggested that theophylline, a phosphodiesterase inhibitor that increases cAMP and cGMP levels, may improve hyposmia. In a study of patients with hyposmia diagnosed by this group's unique standards, treatment of oral theophylline showed improvement in subjective smell loss in 50% of the patients.[83] In a small follow-up study, the use of intranasal theophylline was added to oral theophylline treatment, and the authors reported an additional improvement in olfaction in 8 out of 10 patients.[84] Despite these positive results, both studies lacked a control group, did not account for spontaneous improvement, and did not adjust for statistical inflation of alpha when using multiple individual *t*-tests, which all together may imply these improvements are not actually statistically significant.

In human studies using validated psychophysical measures, in seven chronic kidney disease (CKD) patients with nutritional deficits, modest improvement was seen using intranasal theophylline.[85]

However, since that time, two randomized controlled trials with high numbers of patients have been carried out for intranasal theophylline delivered via irrigation, at both a random concentration and a concentration deemed high enough to show benefit, but in neither was there a significant change in the psychophysical measure of the smelling ability.[86,87]

Additionally, a study in mice evaluating theophylline as a possible therapy actually demonstrated decreased amplitudes in electro-olfactogram (EOG) with the addition of theophylline instead of increased amplitudes in EOG.[88] A reduction of EOG amplitude has been shown to reflect a decrease of olfactory intensity ratings in humans.[89] For these reasons, the author does not recommend this as an option to her patients.

## 5.5.9 Oral Zinc

Zinc therapy for olfaction has been a controversial and largely disproven treatment for olfactory loss. A noncontrolled, retrospective parallel clinical trial study by Aiba et al in 1998 compared zinc sulfate treatment either alone or with a topical corticosteroid and vitamin B or with only steroid and vitamin B.[90] Patients were treated with 300-mg zinc daily for over a month and there was no statistical difference between the groups in patients with postviral or unknown etiologies of hyposmia. In a more recent prospective, randomized study, patients suffering from posttraumatic hyposmia were randomized to either zinc gluconate treatment with high-dose steroids, zinc treatment alone, prednisolone alone, or no treatment. The olfactory recovery rates were significantly higher in the groups with zinc and prednisolone or zinc alone, suggesting that zinc may have a role specifically in treating traumatic anosmia.[68] However, the initial hopes for more generalizable oral zinc treatment were diminished after Lyckholm et al performed a double-blinded, placebo-controlled randomized clinical trial concluding that oral zinc did not offer any benefit to smell or taste in patients whose smell loss was due to chemotherapy.[91]

Conversely, intranasal topical zinc has become a clear problem. Historically a treatment for URIs, zinc nasal sprays were then shown to be a cause of anosmia in mice and humans associated with a burning sensation and complete and irreversible

loss of smell. These products have been ordered off the market by the Food and Drug Administration (FDA), but unfortunately some are still commercially available.[92,93]

### 5.5.10 Alpha-Lipoic Acid

Alpha-lipoic acid and its active metabolite dihydrolipoic acid have been purported to be promising treatments for hyposmia due to olfactory neuron damage as both compounds stimulate expression of nerve growth factor and enhance the conduction velocity of motor nerves.[94] In one study, lipoic acid was ingested orally at 600 mg/d for an average of 4.5 months in a small study with 23 hyposmic patients following URI. There was a moderate to significant improvement in olfaction in 61% of the group. However, as the authors themselves noted, URI-induced hyposmia may have a high rate of spontaneous improvement that would necessitate a proper control group to make true predictions on the efficacy of lipoic acid.

### 5.5.11 Vitamin A Derivatives

Several studies have investigated the role of Vitamin A and its derivatives (retinoids) based on initial studies in animal models that showed increased olfaction regeneration with treatment of retinoic acid.[95] However, a double-blind, placebo-controlled randomized clinical trial performed by Reden et al in patients with postinfectious and posttraumatic olfaction loss found that oral vitamin A did not improve olfactory loss.[96]

## 5.6 Taste

Similar to smell disorders, taste disorders (dysgeusia) can also be differentiated into qualitative and quantitative disorders. Qualitative disorders include parageusia (incorrect tastes elicited by a stimuli that do not correlate with the source) and phantogeusia (unpleasant tastes in the absence of stimulus). The quantitative disorders include ageusia (loss of ability to taste), hypogeusia (partial loss of taste), and hypergeusia (enhanced ability to taste).[97]

## 5.7 Epidemiology and Anatomy

### 5.7.1 Epidemiology

More than 5% of the U.S. adult population self-reported experiencing a taste disorder in the last 12 months.[86] As in olfactory dysfunction, increased age was associated with a higher prevalence of taste dysfunction, but there was no difference in gender prevalence for either chemosensory dysfunction.

### 5.7.2 Anatomy

In humans, the lingual taste buds are found in the fungiform papillae present in the anterior two-thirds of the tongue as well as the circumvallate and foliate papillae in the posterior tongue. The taste buds of the tongue as well as the soft palate, uvula, pharynx, larynx, epiglottis, and esophagus, all contain gustatory receptor cells. These receptors are innervated by afferent neurons that carry out the transduction of five taste stimuli: sour, salty, bitter, sweet, and umami. Taste sensations are transported by three cranial nerves: facial, glossopharyngeal, and vagus nerves. Additional taste receptors are found in the small intestine and these support in recognizing sensations of temperature, texture, and spiciness of food via the trigeminal nerve. With this complex neural involvement, it is rare to experience complete ageusia, and injury to one nerve may go unnoticed in its impact on taste.[98] Aging and smoking can result in gustatory loss due to the reduction in density of fungiform papillae in the taste buds.[99]

In recent years, a taste bud stem cell population has been identified in mice, and the molecular pathways of taste bud development have been elucidated to involve both the sonic hedgehog (Shh) and canonical Wnt/β-catenin pathways.[100] Taste receptors have also emerged as having a role in the innate immune defense system of the upper airway.[101]

## 5.8 Pathophysiology

### 5.8.1 Taste Disorders

The etiology of taste orders is varied and often unable to be determined. The three most frequent causes of taste disorders are idiopathic (34%), posttraumatic (24%), and iatrogenic/post-operative (15%).[85] Of the known etiologies, the main reasons for taste loss are cerebral vascular injury, infection or URI, chronic disease, toxin exposure, iatrogenic (surgery, radiation, and dental operations), medications, and burning mouth syndrome (BMS).

### 5.8.2 Iatrogenic

Middle ear surgery with subsequent injury or transection of the chorda tympani nerve can cause taste impairment. Dental procedures and oral surgeries including tonsillectomies can cause injury to the lingual or inferior alveolar nerve. Chemotherapy and radiation to the head and neck may result in long-term dysgeusia as well as olfactory loss and these side effects are important to counsel patients about pretreatment. Xerostomia (dry mouth), dysphagia, and poor dentition from radiation treatment contribute to loss or altered sense of taste. However, with the use of intensity-modulated radiotherapy (IMRT), greater than 80% of head and neck cancer patients are now reporting normal or near-normal taste function at 3 and 5 years posttreatment.[102]

### 5.8.3 Burning Mouth Syndrome

BMS is a chronic pain syndrome and diagnosis of exclusion that presents with burning of the oral mucosa and is commonly associated with dysgeusia, paresthesia, dysesthesia, and xerostomia.[103] The pathophysiology of BMS is unknown but thought to be neuropathic in origin and usually presents in postmenopausal females, often comorbid with nutritional deficiencies and psychological disorders.

### 5.8.4 Chronic Disease and Deficiencies

URIs are a common culprit for acute dysgeusia in association with olfactory loss. Other chronic diseases that alter the sense

of taste include diabetes and hypothyroidism.[86] Similar to smokers, diabetics have been found to have higher electrogustometric thresholds and lower density of fungiform papillae compared to controls.[104]

Patients with CKD are prone to a uremic state that affects salivary flow and cause dry mouth leading to dysgeusia. These patients are also prone to vitamin deficiencies that may heighten the chemosensory loss. The primary vitamin deficiency associated with taste disorders is zinc deficiency. Zinc deficiency is defined as a plasma concentration of less than 15 µmol/L.[105] However, the use of zinc as a treatment for dysgeusia remains equivocal.

### 5.8.5 Loss of Smell

The sense of "taste" is closely linked to the sense of smell through retronasal olfaction. Often, patients who complain of "abnormal taste" are actually suffering from retronasal olfactory dysfunction, as any appreciation for the flavor of food outside the basic tastes noted above is dependent on the olfactory system.[5] When the author speaks with her patients, she will typically reserve the word "taste" for discussing issues related to the tongue, oral cavity, and the nerves innervating that area, whereas "flavor" is used to discuss the loss of this sense related to loss of smell and the olfactory neurons.

## 5.9 Diagnostic Workup

Gustatory testing is performed either as a whole-mouth test (WMT) or a regional test (RT). In both tests, either chemical or electric stimuli are used. Chemical solutions or tablets are applied in increasing concentrations to different areas of the tongue (RT) or as a swish solution (WMT) using four fundamental tastes of sour, sweet, salty, and bitter.[106] A frequently used technique is the "three-drop test"; three drops of liquids are presented, one of which is the test substance and the other two are pure water. Threshold is defined as the concentration at which the patient identifies the taste three times consecutively. In electrogustometry, an electric stimulus can be used to cause hydrolysis of saliva and for stimulating the gustative chemoreceptors to produce a taste recognized by the patient.[3]

## 5.10 Treatment

Various homeopathic and vitamin treatments have been used in taste disorders without conclusive evidence of their efficacy. These include the use of zinc compounds, alpha-lipoic acid, pilocarpine, transcranial magnetic stimulation, gingko biloba, and acupuncture. A Cochrane review evaluated the literature on the management of patients with taste disturbances.[107] Nine randomized control trials studied the use of zinc supplements, while one assessed the benefits of acupuncture. There was low-quality evidence that zinc supplementation could improve overall taste acuity in patients with zinc deficiency or idiopathic taste disorders as well as insufficient evidence to show that zinc supplements could improve taste perception or acuity in the general public. Acupuncture may show some benefit in taste discrimination, but the study was limited in its size and there is not sufficient evidence to make conclusions on the efficacy of acupuncture in taste disorders. Similarly, bitter mouth syndrome treatment has been studied but also without uniform guidelines. Current treatment options based on only equivocal results include alpha-lipoic acid, gabapentin, and clonazepam, but again, none of these show clear evidence of efficacy.[90]

As cancer therapies advance, there has also been increased focus on the quality of life with cancer treatments including improving taste dysfunction associated with chemotherapy and radiation. Efforts are being made to selectively target the Wnt/β-catenin pathway that is overactive in many cancers while preserving the components of the pathway critical for taste cell progenitor differentiation.[99]

## 5.11 Conclusions

Chemosensory disorders including olfactory and gustatory dysfunction are common and often underdiagnosed in the general population. They are more prevalent with increasing age and significantly affect a patient's quality of life and safety. These disorders can herald early neurodegenerative disease, nasal masses, or sinonasal disease. Evaluation of taste and smell disorders should include a thorough head and neck examination with nasal endoscopy as well as psychophysical testing. Currently, there are few treatment options for olfactory loss and no treatment options for isolated taste loss that have been well validated, although there are many investigational drugs and therapies. Olfactory training, high-volume steroid irrigations, omega-3, and PRP injections are the only beneficial therapies for olfactory dysfunction with strong evidence based on randomized controlled trials.[108] The field for further research in chemosensory dysfunction is wide open, and we hope further investigations in this field will provide more insight into treating the disorders of olfaction and gustation.

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