

## CLINICAL REVIEW

## Olfactory Loss and Beyond: A Practical Review of Chemosensory Dysfunction

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**Background:** Our ability to smell and taste is dictated by 3 chemosensory systems with distinct physiologic mechanisms – olfaction, gustation, and chemesthesis. Although often overlooked, dysfunction of these special senses may have broad implications on multiple facets of patients' lives –including safety, nutritional status, quality of life, mental health, and even cognitive function. As “loss of smell or taste” emerged as a common symptom of coronavirus disease 2019 (COVID-19), the importance of intact chemosensory function has been thrust into the spotlight. Despite the growing recognition of chemosensory dysfunction, this already highly prevalent condition will increasingly impact a larger and more diverse population, highlighting the need for improved awareness and care of these patients.

**Methods:** Contemporary review of chemosensory function and assessments.

**Conclusions:** Although patient-reported chemosensory function measures highlight the ease of screening of chemosensory dysfunction, self-reported measures underestimate both the prevalence and degree of chemosensory dysfunction and do not adequately distinguish between olfaction, gustation, and chemesthesis. Meanwhile, psychophysical assessment tools provide opportunities for more accurate, thorough assessment of the chemosenses when appropriate. Primary care providers are uniquely situated to identify patients burdened by chemosensory dysfunction and raise patient and provider awareness about the importance of chemosensory dysfunction. Identification of chemosensory dysfunction, particularly olfactory dysfunction, may raise suspicion for many underlying medical conditions, including early detection of neurodegenerative conditions. Furthermore, identification and awareness of patients with chemosensory dysfunction may help primary care providers to identify those who may benefit from additional therapeutic and safety interventions, or consultations with specialists for more detailed evaluations and management. (J Am Board Fam Med 2022;35:406–419.)

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## Introduction

Olfaction, gustation, and chemesthesis are unique sensory functions with broad implications on daily

life, ranging from the perception of danger signals (eg, smoke) to the psychosocial implications related to the experience of food.<sup>1–4</sup> Olfaction and gustation are the senses of smell and taste, respectively. Many olfactory and gustatory stimuli also activate the trigeminal nerve, resulting in chemesthesis. Chemesthesis, or trigeminal function, is a type of somatosensory stimulation which includes sensations of touch, temperature, pain, spice, and astringency.<sup>5</sup> Though mediated by separate cranial nerves, these

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chemosenses interact, such as in the perception of food, as the combined chemosensory input makes up what we perceive as “flavor.”<sup>6</sup> Although the chemosenses are associated with unique receptors with different physiologic mechanisms, these functionally distinct senses are intimately intertwined.<sup>7</sup>

Chemosensory dysfunction occurs with alteration in any component of these 3 chemosenses and occurs in a wide variety of clinical settings, including upper respiratory infections (eg, SARS-CoV-2), sinonasal disorders, neurodegenerative diseases, post-traumatic states, and even normal aging, among other etiologies. Though chemosensory dysfunction was thrust into the spotlight during the COVID-19 pandemic, it was already highly prevalent before the pandemic and will only continue to increase. This is in part due to prolonged post-COVID chemosensory aberrations, but also because of an increasingly aged population with alterations due to age-related losses and various medical conditions (eg, diabetes and dementia).

Chemosensory dysfunction can alter our perception of food, but beyond the implications for diet and nutritional status, there are many other significant consequences. The chemosenses are also crucial for detection of toxic exposures, such as smoke, natural gas, and spoiled food.<sup>8</sup> Dysfunction in olfaction, gustation, and chemesthesia have broad psychosocial implications, with significant impacts on patients’ quality of life, depression and anxiety, and cognition.<sup>1-4</sup> Olfaction, in particular, has been repeatedly shown to be a strong and independent predictor of a lack of physiologic resilience to health stressors (ie, frailty) and mortality.<sup>9-11</sup>

Acknowledging its increasing prevalence and broad implications, identification and understanding of chemosensory dysfunction offers a significant opportunity to impact patient care. Although primary care providers (PCPs) are uniquely situated to identify patients with new-onset chemosensory function changes, they generally lack formal training in these unique senses. This review provides practical insights into the distinct but overlapping physiologic mechanisms of the chemosenses, highlights common etiologies of chemosensory dysfunction, increases awareness of accurate and clinically feasible chemosensory assessment tools, and provides suggestions for chemosensory assessment and management in the primary care setting.

## Chemosensory Physiology and Prevalence of Dysfunction

### Olfaction

Olfaction begins with the entry of odorants into the nose, specifically the olfactory cleft, via 1 of 2 routes—orthonasal or retronasal.<sup>12</sup> Orthonasal olfaction occurs as odorants pass through the nares to reach the olfactory cleft.<sup>12</sup> In contrast, retronasal olfaction occurs as odorants within the oral cavity traverse the nasopharynx—especially during swallowing, mastication, or nasal exhalation—to reach the olfactory cleft.<sup>12</sup> Once odorants reach the olfactory cleft, they contact olfactory epithelium, which lines the cleft between the nasal septum and superior and middle turbinates.<sup>13</sup> The olfactory epithelium contains dendritic knobs and cilia of olfactory cells containing olfactory receptors, as well as axons of olfactory neurons that travel through the cribriform plate before synapsing at the olfactory bulb. The interaction of odorants with olfactory receptors sends signals to multiple areas of the brain, allowing for processing and interpretation of odorants.<sup>14</sup>

Given that the olfactory system is composed of peripheral neurons which reconnect centrally, there is remarkable capacity for regeneration. Damage occurs continuously throughout life, but proliferation of stem cells allows for regular repair of olfactory function.<sup>15</sup> Despite this regenerative potential, olfactory loss can still occur and is classified based on 3 pathophysiologic mechanisms – conductive, sensorineural, or mixed.<sup>15</sup> Conductive loss occurs when odorants are physically blocked from the olfactory epithelium by pathology such as nasal polyps or mucosal edema.<sup>15</sup> Sensorineural loss occurs with olfactory neuroepithelium damage or dysfunction, while central loss occurs through damage or disruption of the olfactory pathways in the central nervous system, and mixed loss occurs when there is overlapping etiologies.<sup>15</sup>

Olfactory dysfunction is extremely common, with an estimated prevalence of 12 to 13% in the US and 25% worldwide.<sup>8,16</sup> Accurate estimations of prevalence have been limited by study size, patient demographics, and variation in dysfunction definitions. Higher rates of olfactory dysfunction have been reported in men compared with women, and in Black individuals compared with White individuals, though trends are not fully understood.<sup>17-19</sup>

Olfactory dysfunction invariably increases with age. Though there is a broad range of prevalence estimates, up to 62.5% of those over age 80 experience olfactory dysfunction.<sup>2,8,20–29</sup> In addition, people tend to underestimate both the prevalence and severity of their olfactory dysfunction on self-report,<sup>8,16,20,30</sup> with 1 study reporting that up to 74.2% of people who had measured olfactory dysfunction did not recognize it clinically.<sup>29</sup> The importance of this for overall health and safety cannot be overstated, as US population-level data revealed adults age 70 and older misidentify smoke and natural gas odors at rates as high as 20.3% and 31.3%, respectively.<sup>8</sup>

### **Gustation**

There are 5 basic tastants—sweet, sour, salty, bitter, and umami (“savory”). Gustation begins with the ingestion of various tastants into the oral cavity, where they are dissolved in saliva. Tastants contact taste buds located on the tongue, palate, pharynx, and larynx.<sup>6,31</sup> On the tongue, taste buds are located in fungiform, foliate, and circumvallate papillae, under a keratinous layer with openings for taste pores.<sup>31</sup> Unlike the receptor neurons in the olfactory system, taste buds are composed of taste receptor cells, not neurons. These taste receptor cells have microvilli that extend through the taste pores to contact tastants.<sup>6</sup> The microvilli contain gustatory receptors, which are stimulated by 1 of the 5 basic taste qualities.<sup>32</sup> Gustatory receptors then send signals to the brain for interpretation of tastants.<sup>6,31</sup> The structural differences between types of gustatory receptors may provide the basis for discrimination between different taste qualities.<sup>32</sup>

Gustatory deficits can be classified by pathophysiologic mechanism.<sup>33</sup> Transport dysfunction occurs when gustatory stimuli cannot contact gustatory receptors due to conditions affecting the oral cavity, such as candidiasis or salivary dysfunction, such as xerostomia.<sup>33</sup> In contrast, sensory dysfunction occurs when gustatory neuroepithelium is damaged, and neuronal dysfunction occurs when relevant peripheral nerves or components of the central nervous system are compromised.<sup>33</sup>

Gustatory dysfunction impacts approximately 17.3% of Americans.<sup>16</sup> Accurate predictions of prevalence are limited by not only variation in patient population, but also the complex interaction of olfaction and gustation. A recent study found that in patients reporting only taste disturbance,

rates of abnormal gustatory function were 25.4%, but rates of olfactory dysfunction were 44.4%.<sup>34</sup> Olfactory dysfunction leading to a perceived gustatory impairment is common, due to the complex interaction of the chemosenses creating the “flavor” of ingested foods and drinks.

### **Chemesthesis**

Chemesthesis occurs when stimuli activate branches of the trigeminal nerve (ophthalmic or maxillary) in the nasal or oral cavity.<sup>5,35</sup> Chemesthesis is the cause of many of the somatosensory sensations we perceive, including temperature (eg, cooling sensation from menthol), spice (eg, from pepper), or even ammonia (eg, from “smelling salts”). Researchers continue to discover receptors involved in chemesthesis, and the physiologic mechanisms of trigeminal function and dysfunction remain an area of active research.<sup>36</sup> The estimated prevalence of chemesthetic dysfunction is limited, but notably, isolated chemesthetic dysfunction is rare and is most often reported in conjunction with olfactory dysfunction.<sup>37–39</sup>

## **Common Etiologies of Acquired Chemosensory Dysfunction**

### **Viral Respiratory Infections**

Acute phases of upper respiratory tract infections (eg, rhinovirus, influenza virus) are among the most frequent causes of chemosensory dysfunction.<sup>40</sup> This became particularly important during the COVID-19 pandemic, as “loss of taste or smell” was noted as a mechanism of detecting otherwise asymptomatic COVID-19 cases.<sup>41,42</sup> Patients typically present with sudden onset chemosensory disturbances with other associated symptoms, such as fever, congestion, and fatigue.

In some instances, the chemosensory dysfunction associated with viral infections may become chronic.<sup>43,44</sup> Postviral olfactory dysfunction (PVOD) is a common cause of chronic olfactory loss.<sup>45–47</sup> The clinical course of PVOD is variable; some patients experience complete resolution of olfactory functioning within months of onset, while others have permanent dysfunction.<sup>48</sup> One study evaluating long-term prognosis of PVOD found that 31.7% of patients had complete recovery of self-reported smell function, and 85.7% had some level of self-reported improvement at least a year from their infection.<sup>49</sup> There is also

evidence that patients with PVOD have associated impaired chemesthesis,<sup>39</sup> which improves with olfactory function.<sup>38</sup>

### **Sinonasal Disease**

Sinonasal disease accounts for ~20% of olfactory dysfunction cases.<sup>50,51</sup> There are various etiologies – including allergic rhinitis (AR) and chronic rhinosinusitis (CRS). AR and CRS affect millions of Americans, and 20 to 40% of AR patients and 70 to 80% of CRS patients experience olfactory dysfunction.<sup>52–59</sup> Loss of olfactory function is a cardinal symptom of CRS. There are multiple possible causes of olfactory dysfunction in CRS, including nasal air-flow obstruction in the setting of CRS with nasal polyps, localized inflammation of the sinonasal and olfactory mucosa in CRS without nasal polyps, both of which may limit the ability for odorants to reach the olfactory cleft and/or bind to olfactory receptors. Though less well characterized, a substantial number of these patients also have independent gustatory dysfunction.<sup>60</sup> In patients with chemosensory dysfunction secondary to sinonasal disease, patients will often present with other symptoms associated with their sinonasal disease process.

### **Posttraumatic**

Posttraumatic chemosensory dysfunction accounts for 10% to 20% and 20% to 25% of olfactory and self-reported gustatory dysfunction patients, respectively.<sup>34,51,61</sup> The prevalence of post-traumatic chemosensory dysfunction increases with increasing head trauma severity and is estimated at 30%.<sup>62–64</sup> It is generally hypothesized that shearing effects of the frontal lobe motion are responsible for the dysfunction due to head trauma.<sup>63</sup> There is also evidence that chemesthetic dysfunction occurs after head trauma, specifically in populations with known olfactory dysfunction.<sup>37,38</sup> Posttraumatic chemosensory disorder may be easier to diagnose as it often presents after a known head trauma.

### **Aging**

As we age, dysfunction occurs across a broad range of sensorineural processes, including vision and hearing, but also olfaction, gustation, and chemesthesis. As mentioned above, chemosensory dysfunction commonly occurs in otherwise healthy individuals during normal aging processes due to a multitude of mechanisms. In the case of

olfaction, age-related dysfunction is due to changes in the peripheral olfactory system, including decreased olfactory receptor neurons, impaired regeneration capacity, and impeded clearance of bacteria, to name a few.<sup>65</sup> Normal aging should be considered on the differential for elderly patients with chemosensory dysfunction.<sup>27</sup>

### **Neurodegenerative Conditions**

Chemosensory dysfunction is common in neurodegenerative disorders, with rates of olfactory dysfunction in Parkinson's disease ranging from 50% to 90%.<sup>66</sup> With gradual onset, and as 1 of the first clinical manifestations of neurodegeneration, chemosensory dysfunction may be a harbinger of multiple neurodegenerative diseases including Alzheimer's, Huntington's, and Lewy body dementia. Multiple studies have linked olfactory dysfunction to later development of cognitive decline,<sup>66–74</sup> and recent studies have also revealed that intact olfactory function is associated with lack of progression to dementia.<sup>75</sup>

### **Idiopathic**

Finally, chemosensory loss is considered idiopathic if no other etiology can be identified after evaluation. Chemosensory dysfunction is idiopathic in 18% and 34% of olfactory and gustatory loss patients, respectively.<sup>50,51,61</sup> These numbers are anticipated to decrease as understanding of chemosensory dysfunction mechanisms and evaluation improves.

### **Types of Chemosensory Assessment**

A variety of assessments have been developed to quantify patients' chemosensory capabilities. Subjective tests require participants to consciously report findings, while objective tests are imaging or electrophysical tests involving recording electric changes after stimuli presentation.<sup>76</sup> Psychophysical tests, on the other hand, have both subjective and objective components. These require more rigorous testing than subjective self-report options but still require subjects to report perceptions of stimuli. Although individual subjective and objective tests are categorized as separately measuring olfaction, gustation, or chemesthesis, it may be challenging to clinically distinguish these senses, as stimuli typically simultaneously activate multiple sensory modalities.<sup>7,76</sup>



## Olfaction

There are multiple validated self-report assessments for the measurement of olfaction.<sup>77–79</sup> These instruments make information easily attainable and are often modified to reflect regional variations in scent awareness, but they are often not closely associated with validated psychophysical tests.<sup>76</sup> As many as 74.2% of healthy individuals with psychophysically measured olfactory dysfunction fail to detect and accurately self-report their sensory deficits.<sup>29</sup> As this data suggests, when physicians ask patients to describe or rate their olfactory dysfunction in general clinical settings, patients' responses may be inaccurate.<sup>29,76,80</sup> Therefore, psychophysical olfactory assessments are the gold standard for olfactory testing because of their accuracy.<sup>81,76,82</sup>

Psychophysical tests most commonly measure odor identification, the ability to detect and accurately recognize a certain odor. Psychophysical tests may also evaluate olfactory discrimination, the ability to distinguish 1 odor from another; olfactory threshold, the lowest concentration of an odorant that can be reliably detected; or olfactory memory, the ability to correctly identify an odor on repeat administration.<sup>76,82</sup> Most of the psychophysical assessments for olfaction focus on the orthonasal route (Table 1).<sup>69,76,81,83–92</sup> Measurements of retronasal olfaction are significantly less developed and are not used in routine clinical practice.<sup>93</sup>

Two commonly used assessments are the 40-item University of Pennsylvania Smell Identification Test (UPSIT) and the “Sniffin’ Sticks.”<sup>76,86,92</sup> The UPSIT is a suprathreshold test that assesses odor identification, which benefits from ease of clinical use, high sensitivity and reliability (test–retest  $r=0.94$ ), and extensive normative data.<sup>76,86</sup> Meanwhile, “Sniffin’ Sticks” evaluates threshold, discrimination, and identification, and provides a composite score (TDI) that describes reliability and psychometric characteristics.<sup>92</sup> Though this instrument is robust, its completion requires increased time and resources, limiting its use in primary care settings.<sup>76,92</sup>

The UPSIT has been abbreviated as the 3-item Pocket Smell Test (PST) and the 12-item Brief Smell Identification Test (B-SIT).<sup>69,83</sup> These shortened assessments allow clinicians to detect chemosensory dysfunction in a time-efficient, cost-effective manner. A subset of olfactory assessments instruments—including the PST and B-SIT—are

self-administered as opposed to clinician-administered, allowing patients to perform the testing at their convenience, which may be advantageous in primary care settings.<sup>69,83–86</sup>

In addition, electroolfactogram, electroencephalography, positron emission tomography, and functional magnetic resonance imaging (fMRI) have all been utilized to measure olfactory function objectively.<sup>94–98</sup> Though these techniques have improved our understanding of olfaction-related cortical networks in research settings, they are not appropriate for clinical olfactory assessment even in tertiary care centers, as they are more invasive and costly, require extensive resources, and have high false positive and false negative rates.<sup>76,95,97</sup>

## Gustation

Measuring the subjective experience of taste is difficult considering the significant contribution of olfaction and trigeminal input to the perception of flavor.<sup>7</sup> Moreover, many individuals who report gustatory deficits oftentimes exhibit measurable olfactory impairment (particularly retronasal olfaction), instead of gustatory impairment.<sup>34,81</sup> As a result, few self-report questionnaires have been used or validated to assess taste in various populations,<sup>99–101</sup> and psychophysical assessments are the most clinically appropriate tests for gustation and allow clinicians to isolate gustatory dysfunction from olfactory dysfunction.<sup>76,102</sup>

Psychophysical assessments often measure identification, the ability to identify stimuli, and threshold, the lowest concentration of stimuli that can be reliably detected.<sup>102</sup> Whole mouth tests assess the subject's entire oral cavity, while regional taste tests isolate dysfunction to specific areas of the tongue.<sup>102–104</sup> As gustatory assessments generally require significant time and resources, they are normally reserved for use by trained specialists (generally at academic institutions), and therefore patients with suspected isolated gustatory dysfunction may warrant referral for further testing. Psychophysical gustatory assessments that PCPs should be aware of are summarized in Table 2.<sup>102</sup>

In addition, electrogustometry is a method of assessing gustatory losses in research settings.<sup>105</sup> This resource intensive instrument is not clinically practical, because it requires specific materials and is not predictive of function in daily life.<sup>102,105</sup>

**Table 1. Olfactory Psychophysical Clinic-Based Assessments**

Instrument	Function assessed	Substances used	Protocol	Advantages	Disadvantages
Brief or Cross-Cultural Smell Identification Test <sup>83</sup>	Identification	Banana, chocolate, cinnamon*, gasoline, lemon, onion, paint thinner, pineapple, rose, soap, smoke, turpentine	Derived from the UPSIT. Using microencapsulated odorants, subjects progress through 12-item multiple-choice test for 12 odors	Requires less time, cost efficient Can be self-administered	Less thorough evaluation
Pocket Smell Test <sup>69</sup>	Identification	Lemon, lilac, smoke	Derived from the UPSIT. Using microencapsulated strips, subjects progress through 3-item multiple-choice test for 3 odors.	Requires less time, cost efficient Can be self-administered	Less thorough evaluation
Q-Sticks <sup>84</sup>	Identification	Cloves*, coffee, rose	Using felt-tip pens with odorants, subjects progress through 3-item multiple-choice test for 3 odors.	Can be self-administered	Less thorough evaluation
Quick Smell Identification Test <sup>85</sup>	Identification	Chocolate, banana, smoke	Using microencapsulated odorant strips, subjects progress through 3-item multiple-choice test for 3 odors.	Can be self-administered	Less thorough evaluation
University of Pennsylvania Smell Identification Test <sup>86</sup>	Identification	Banana, bubble gum, cedar, cheddar cheese, cherry, chocolate, cinnamon*, cloves*, coconut, dill pickle, fruit punch, gasoline, gingerbread, grape, grass, leather, lemon, lilac, lime, licorice, menthol*, mint, motor oil, natural gas, onion, orange, peach, peanut, pine, pineapple, pizza, root bear, rose, smoke, soap, strawberry, thinner, turpentine, watermelon, wintergreen*	Using scratch and sniff scented strips, subjects progress through 40-item multiple-choice test for 40 odors.	High sensitivity and reliability; extensive normative data Can be self-administered	More time intensive
Snap & Sniff Threshold Test <sup>87</sup>	Threshold	PEA, dilutions ranging from 10 <sup>-2</sup> (strongest) to 10 <sup>-9</sup> (weakest) volume/volume concentrations	The kit contains 20 smell “wands.” Five contain no smell, while the other 15 contain PEA dilutions. Examiners plan the wand under subjects’ noses and briefly present the dilution scent. A single staircase forced-choice paradigm is recommended.	Time efficient, rapid assessment of general olfactory function Newer test but recently validated	Less thorough evaluation – only evaluates detection threshold
Alcohol Threshold Test <sup>88</sup>	Threshold	Ethyl alcohol (10%, 25%, 50%, 70%, 96%)	Examiners place 100 mL bottles with saline and with varying concentrations of ethyl alcohol under subjects’ noses. The threshold scores of 1, 2, 3, 4, and 5 correspond to the weakest detectable alcohol concentrations of 10%, 25%, 50%, 70%, and 96%, respectively. The threshold score of 6 corresponds to participants not detecting 96% alcohol.	Time efficient, rapid assessment of general olfactory function	Less thorough evaluation Requires clinician administration
Smell Threshold Test <sup>89</sup>	Threshold	Polypropylene, PEA	Examiners place 120 mL polypropylene squeeze bottles with mineral oil and varying concentrations of PEA in mineral oil under		Less thorough evaluation Requires clinician administration

*Continued*

Table 1. Continued

Instrument	Function assessed	Substances used	Protocol	Advantages	Disadvantages
"Sniffin' Sticks" <sup>90</sup>	Identification, discrimination, threshold	Apple, anise seed, banana, cinnamon*cloves*, coffee, fish, garlic*, lemon, licorice, orange, peppermint*, pineapple, rose, shoe leather, turpentine, n-butanol	subjects' noses. The threshold is the mean of the last 4 of 7 staircase reversals. Using felt-tip pens with odorants, subjects progress through 16-item multiple-choice test of 16 odors for identification, triple forced choice for 16 pairs of odorants for discrimination, and the presentation of n-butanol in varying concentrations for threshold. Threshold was calculated as the mean of the last 4 of 7 staircase reversals.	Enables testing of three smell domainsCan be self- or clinician-administered	More time intensive

Abbreviations: PEA, phenyl ethyl alcohol; UPSIT, University of Pennsylvania Smell Identification Test.

\* Indicates potential olfaction and chemesthesis overlap.

### Chemesthesis

Clinicians are increasingly developing assessments to specifically measure chemesthesis.<sup>106</sup> Currently, there are no validated, self-report questionnaires which solely focus on assessing trigeminal function. However, targeted questions have been used to attempt to distinguish olfactory, gustatory, and chemesthetic functions.<sup>106</sup> Chemesthetic function can be evaluated psychophysically by evaluating subjects' ability to lateralize trigeminal stimulation (Table 3).<sup>107,108</sup> Two new psychophysical assessments of chemesthesis have been reported since 2016, both of which are awaiting validation (Table 3).<sup>109,110</sup> The further development and utilization of such assessments provides an opportunity to standardize trigeminal function testing, but these tests are not currently appropriate for routine clinical use.<sup>102</sup>

### Chemosensory Testing in Primary Care Settings

Chemosensory function is an underrecognized but critical contributor to patients' overall health and quality of life, specifically impacting patients' nutritional status, safety around fire or toxins, and overall psychological well-being.<sup>3,4</sup> Hearing and sight frequently come to mind as vital human sensory functions, but studies suggest that olfactory dysfunction is independently associated with an increased risk of dementia, frailty, and all-cause mortality.<sup>9–11,28,68,69,111</sup> Besides the known psychosocial effects of chemosensory dysfunction, this underscores the increasingly recognized connection between chemosensory function and other domains of health, such as physical and cognitive function. As interventions which improve patients' chemosensory functioning are associated with improved quality of life, the identification and management of chemosensory dysfunction should be an important element of comprehensive care.<sup>112,113</sup>

For patients with chemosensory dysfunction, as with any patient encounter, it is of the utmost importance to first perform a comprehensive history and physical. History should focus on identifying risk factors (eg, age, recent head injury) and characterizing the chemosensory dysfunction (eg, sudden onset, associated symptoms) to help distinguish between common types of chemosensory dysfunction. Patients should also be screened for warning signs such as epistaxis, headache, vision changes, or

**Table 2. Gustatory Psychophysical Clinic-Based Assessments**

Instrument	Function assessed	Substances used	Protocol	Advantages	Disadvantages
Whole mouth evaluation					
Taste sprays	Identification	Substances diluted in 100 mL distilled water: sweet (10g D-sacharose), sour (5g citric acid), salty (7.5g NaCl), bitter (0.025g quinine hydrochloride), and umami (4g MSU)	Patients open mouth for spray application and close mouth as they identify flavor. Patients receive 1 point for each correctly identified taste. The score is graded 0 to 5.	Indicates whether “suprathreshold” taste perception has been preserved, provides overall taste quality perception data, short time needed for testing, good reproducibility of results, long shelf life	Examiners cannot test individual parts of the oral cavityRequires clinician administration
“Sip and spit” tests	Identification	Patients imbibe flavors from cups or other vessels and then report on the detected flavor.			
Regional evaluation					
Taste strips	Identification, threshold	20 taste-impregnated filter-paper strips presented in randomized order with taste qualities in increasing concentrations: sweet (0.4, 0.2, 0.1, 0.05 g/mL sucrose), sour (0.3, 0.165, 0.09, 0.05 g/mL citric acid), salty (0.25, 0.1, 0.04, 0.016 g/mL NaCl), bitter (0.006, 0.0024, 0.0009, 0.0004 g/mL quinine hydrochloride), and umami (0.25, 0.1, 0.04, 0.016 g/mL MSG)	Patients identify the taste quality on a form. Patients receive 1 point for each correctly identified taste. The score is graded 0 to 20. An overall score $\leq 9$ is considered hyposgeusia.	Allows examiners to test each side of the tongue independently, provides basic data on detection threshold and intensity of flavor, short time needed for testing, good reproducibility of results, long shelf life	Certain areas of the tongue may be difficult to isolate or reach with strips or dropsRequires clinician administration

Abbreviations: MSG, monosodium glutamate; MSU, monosodium urate; NaCl, sodium chloride.



**Table 3. Chemesthesis Psychophysical Assessments**

Instrument	Function assessed	Substances used	Protocol	Advantages	Disadvantages
Stimuli lateralization <sup>108</sup>	Lateralization	Benzaldehyde, eucalyptol	Subjects were presented with two bottles, one for either nostril. Bottles are filled with chemicals dissolved in propylene glycol or propylene glycol alone. A 15 mL puff of air from each bottle is simultaneously administered into one nostril. Subjects report which nostril was presented with the stimuli.	Simple administration, distinguishes olfactory function from chemesthesis	Requires clinician administration, protocol requires ~30 minutes per stimuli
Odorant Detection Test <sup>110</sup>	Detection threshold, discrimination, identification, lateralization	Camphor, diallyl sulfide, ethanol, eucalyptol, menthol, propranolol	Using felt-tip pens with chemicals dissolved in propylene glycol, subjects progress through identification of the sensation quality and triple-forced-choice procedure for discrimination for the 6 chemicals. Threshold and lateralization were assessed with menthol. Threshold was calculated as the mean of the last 4 of 7 staircase reversals.	Simple administration, similar protocol to Sniffin' Sticks	Not validatedRequires clinician administration
CO <sub>2</sub> device <sup>111</sup>	Pain responsiveness	CO <sub>2</sub> stimuli with various durations (multiples of 50 ms)	CO <sub>2</sub> stimuli is provided through standard nasal cannula in 10 seconds intervals. With each interval, stimulus duration is increased by 50ms until the subject pushes a button, indicating a painful sensation.	Assesses "mass of a stimulus" rather than concentration	Not validatedRequires clinician administration

watery rhinorrhea, which may indicate a more malignant process and warrant expedited referral and assessment. A thorough head and neck examination should be performed, as well as a full neurologic examination. PCPs should consider the possible etiologies of a patient's chemosensory dysfunction and tailor their assessment based on this to develop a plan for work up and management of chemosensory dysfunction. Notably, this review focuses on acquired forms of chemosensory dysfunction, but congenital forms such as Kallmann syndrome and congenital anosmia are possible, and a lifelong history of dysfunction would be present.<sup>114,115</sup>

Simply by identifying patients with self-reported chemosensory dysfunction and performing an initial history and physical, PCPs can improve patient care by providing specialist (ie, otolaryngologist) referrals for further management. In addition, patients at risk for associated conditions, including anxiety and depression, can be identified and treated as indicated. For PCPs interested in performing additional testing in their practice, psychophysical chemosensory tests can be administered quickly and inexpensively with few, if any, risks to the patient. As the value of time cannot be overstated in the primary care setting, we recognize the importance of brevity in these tests and therefore recommend the use of a short, psychophysical olfactory assessment that can be self-administered by patients, such as the abbreviated B-SIT. Finally, for those with the resources necessary to implement such a change, routine chemosensory dysfunction screening in certain at-risk populations (eg, elderly populations) may raise awareness and provide opportunities to educate patients about the risk factors associated with dysfunction and advise on how to improve safety and overall quality of life. Given the association of chemosensory dysfunction and dementia progression, the utility of routine chemosensory testing in the elderly is currently being investigated,<sup>116</sup> and there is some evidence that evaluation of olfactory function subscores may help distinguish neurodegeneration from normal aging.<sup>117</sup>

### Management of Chemosensory Dysfunction

In patients with identified chemosensory dysfunction, management should first begin with safety counseling, with emphasis on using smoke/natural gas detectors, monitoring food expiration dates,

and maintaining proper nutrition. In many cases, relying on family or friends for assistance in monitoring for food spoilage or for hygiene may be necessary. Patients should also be counseled on the possible etiologies of their chemosensory dysfunction, and the associated psychosocial implications. Although many patients with olfactory dysfunction may have some improvement in olfaction without treatment, many chemosensory deficits are longstanding. Efficacious treatment options are limited, but treatment of the inciting pathology is generally an appropriate first approach. For example, treatments for CRS without nasal polyps and AR with topical steroids may improve inflammation and thereby improve conductive olfactory dysfunction.<sup>53,55,118,119</sup> On the other hand CRS with nasal polyps may require systemic steroids to notice clinical improvement. In addition, patients with gustatory dysfunction from throughsh may benefit from antifungals and improved oral hygiene.<sup>120</sup>

In patients with olfactory dysfunction, olfactory training represents a novel treatment strategy for a variety of olfactory loss etiologies.<sup>45,121–125</sup> Olfactory neurons demonstrate neuroplasticity, and similar to physical therapy after a stroke, olfactory training aims to strengthen and “retrain” neural pathways.<sup>112,125</sup> Radiologic studies suggest that the olfactory system may be strengthened by the act of practicing sniffing alone, with 1 study demonstrating an increased in signal intensity in the olfactory network on fMRI following olfactory training.<sup>122</sup>

Most olfactory training regimes use twice daily sessions including 1 scent from each of 4 odor categories: flowery, fruity, spicy, resinous—commonly with essential oils. Though recommendations regarding timeline, duration of therapy, and adjunctive use of topical steroids are varied, it is generally agreed on that earlier initiation of olfactory training following olfactory loss is associated with improved outcomes.<sup>45,50,112,125</sup> It may take 3 months to 6 months of olfactory training before patients notice an improvement and communicating this may aid in compliance.<sup>45</sup>

Additional therapies have been trialed with varying success, including topical or systemic steroids, nonsteroidal topicals, and nonsteroid oral medications (eg, vitamins, antioxidants, antibiotics, phosphodiesterase inhibitors).<sup>45</sup> There have been studies demonstrating benefit, no improvement, or no obvious conclusion in multiple of these

modalities.<sup>45</sup> Given additive risks of additional treatments, it is important to carefully consider which patients may benefit from additional medical therapies. In patients who are having persistent chemosensory dysfunction despite treatment, or those with significant consequences of their chemosensory dysfunction (eg, depression), referral to the proper specialist is warranted for more complex work up or management. For example, referral to an otolaryngologist would allow for a more thorough head and neck examination, including nasal endoscopy to determine if a lesion is present.

## Conclusion

The 3 chemosensory functions of olfaction, gustation, and chemesthesis have distinct but overlapping physiologic mechanisms. Chemosensory dysfunction has broad implications and is therefore an important aspect of patients’ health. Identification and management of chemosensory dysfunction allows for safety education and risk stratification, as olfactory loss may occur on a continuum from healthy patients, to ill (ie, frail) patients, to even death. Awareness and screening for chemosensory dysfunction in primary care settings can enable PCPs to provide more comprehensive medical care.

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