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Clinical Diagnosis and Current Management Strategies for Olfactory Dysfunction
A Review

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IMPORTANCE Olfactory dysfunction affects approximately 20% of the general adult population. It is associated with reduced quality of life and important health care outcomes such as neurodegeneration and death. The accurate diagnosis of olfactory dysfunction is therefore important to quantify impairment, the effect of intervention, and residual disability. This review summarizes the current evidence on the diagnosis and management of olfactory dysfunction.

OBSERVATIONS Olfactory dysfunction can be quantitative and/or qualitative. Despite numerous underlying pathophysiological causes, approximately two-thirds of cases are due to sinonasal disease or postinfectious or posttraumatic dysfunction. All patients should undergo assessment with a thorough clinical history and examination (including nasoendoscopy) followed by subjective olfactory assessment and some form of validated psychophysical test. Psychophysical tests should include assessment of odor threshold and/or odor discrimination or identification, although multicomponent testing has diagnostic advantages. Imaging of the olfactory tract and brain is indicated for a high index of suspicion for intracranial pathology. Treatment with olfactory training may benefit patients with nonsinonasal dysfunction. Treatment with medications such as phosphodiesterase inhibitors or intranasal sodium citrate require further research, as do nonchronic rhinosinusitis–related surgical procedures.

CONCLUSIONS AND RELEVANCE This multifactorial assessment and patient olfactory training may improve the accuracy and reliability with which olfactory dysfunction is diagnosed and monitored.

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In recent years, the importance and frequency of olfactory dysfunction has become apparent. Now known to affect approximately 20% of the general adult population,[1] impaired olfactory function can have a significant effect on quality of life through disordered eating behaviors, deficits in olfactory-mediated social behavior, and environmental hazard exposure. Although such effects are often more extreme in individuals relying professionally on their sense of smell, the more insidious effect of dysfunction leads to symptoms of depression in as many as 40% of patients.[2] Moreover, the physiological importance of smell is revealed by the association between olfactory dysfunction and disease. Olfactory dysfunction is an early biomarker in many neurodegenerative conditions, including Alzheimer disease and Parkinson disease, and anosmia is more closely associated with 5-year mortality than myocardial infarction, cerebrovascular accident, diabetes, heart failure, or cancer.[3,4]

Therefore, olfactory dysfunction should be diagnosed early, and treatment should be offered where available. The recent Position Paper on Olfactory Dysfunction[5] was published to provide guidance on the diagnosis, monitoring, and evidence-based management of olfactory impairment. In the following review, we provide an overview of the content of these guidelines.

Pathophysiology and Clinical Presentation

General Overview of Smell

The perception of smell requires activation of olfactory receptor neurons (collectively, cranial nerve I) found within the neuroepithelium of the olfactory cleft. Depending on the odor, this perception is usually accompanied by activation of the trigeminal nerve (cranial nerve V), which imparts varying amounts of heat, coolness, pungency, and irritation. Perception of odors transmitted through the nose during breathing or sniffing is termed *orthonasal olfaction*, whereas perception of those transmitted through the nasopharynx during eating is *retronasal olfaction*. Normal olfactory function is termed *normosmia*.

Olfactory dysfunction is broadly divided into quantitative and qualitative disorders. Quantitative dysfunction denotes reduced ability to perceive odors, without distortion in their quality. This type of dysfunc-

tion can be further subdivided according to severity into *hyposmia*, in which the perception of odor stimuli is reduced but not absent, and *functional anosmia*, in which the patient does not have sufficient residual function to have any meaningful olfactory perception.

Qualitative olfactory dysfunction normally coincides with quantitative dysfunction and can itself be further divided into *parosmia* and *phantosmia*. Parosmia is the distortion of an odor stimulus, usually to a more unpleasant quality. Phantosmia is the perception of an odor (again usually negative in quality) in the absence of a stimulus.

Specific anosmia refers to the inability to smell particular odors and is thought to be a normal physiological trait.[6] *Hyperosmia* is the enhanced perception of smell, which is extremely rare but has been reported to be associated with some neurological conditions.

Olfactory Dysfunction

Approximately 200 different causes for olfactory dysfunction are thought to exist. However, among cases presenting to specialist clinics, more than two-thirds are due to sinonasal disease or postinfectious or posttraumatic olfactory dysfunction.[7]

Impairment secondary to sinonasal disease is most commonly caused by chronic rhinosinusitis (CRS) with or without nasal polyposis. Indeed, olfactory dysfunction is thought to affect 61% to 83% of patients with CRS irrespective of subtype and up to 95% of those with nasal polyposis. In addition to mechanical obstruction of odorants to the olfactory cleft caused by edema and polyps, impairment in CRS can also be attributed to inflammatory cytokine-mediated olfactory receptor dysfunction, as well as histological remodeling of the neuroepithelium with more established disease. Patients with this form of dysfunction most commonly describe a gradual onset of quantitative impairment (parosmia and phantosmia are rare) that fluctuates in severity over time. Without treatment, olfactory dysfunction secondary to sinonasal disease is unlikely to improve spontaneously.[5]

Postinfectious olfactory dysfunction (PIOD) is a common form of impairment that occurs after upper respiratory tract infection. The pathophysiology of PIOD is poorly understood but may involve damage at the level of the olfactory neuroepithelium, the olfactory nerve, or olfactory-eloquent areas within the central nervous system. The latter is thought to be possible through direct transmission of pathogens to the brain via the olfactory nerve. The causative agent is usually viral and most often produces symptomatic infection in middle-aged or older women. However, some patients may experience dysfunction after a minimally symptomatic or asymptomatic infective episode, the latter potentially leading to an incorrect diagnosis of idiopathic olfactory dysfunction. Onset tends to be sudden, fluctuation in function is unusual, and qualitative dysfunction (particularly parosmia) often occurs in addition to quantitative loss. Longitudinal series have demonstrated spontaneous recovery in approximately one-third of patients.[5]

Posttraumatic olfactory dysfunction (PTOD) occurs after head injury and is a common presentation to specialist clinics. The underlying pathophysiological mechanism may be 1 or a combination of the following: (1) impaired odorant access to the olfactory cleft (secondary to deforming nasal bone and/or septal fractures, blood clots, edema, and direct injury to the neuroepithelium); (2) transection or shearing of olfactory nerve fibers as they cross the cribriform plate (which requires higher-force coup-contrecoup injury or trauma to the midface and/or anterior skull base); and (3) intraparenchymal injuries and subsequent gliosis within olfactory-eloquent brain regions. Onset may be immediately after injury or may be delayed. Delayed onset may be attributed to lack of awareness until the patient returns to their normal environment or experiences progressive central pathology (eg, edema and/or gliosis). Posttraumatic olfactory dysfunction causes more severe quantitative impairment than other common forms of dysfunction and has a worse prognosis for spontaneous recovery, although this outcome is possible. In addition to quantitative impairment, patients with PTOD may experience qualitative dysfunction, particularly phantosmia.[5]

Other causes of olfactory dysfunction include neurological disorders (particularly neurodegenerative conditions such as Alzheimer disease and Parkinson disease), toxins and medications, congenital disorders (syndromic and nonsyndromic), iatrogenic injuries, and normal aging. Where a cause for impairment cannot be found despite careful history, examination, and investigation, a diagnosis of idiopathic impairment can be made.

Assessment and Diagnosis

History and Examination

Clinical assessment of patients with olfactory dysfunction should include a thorough history and full ear, nose, and throat examination. During history taking, general points such as onset of dysfunction, progression, fluctuation, and severity should be documented, as well as presence of parosmia and phantosmia. Precipitating events and associated symptoms should be recorded. In older adults, the possibility of neurodegeneration should be kept in mind and questioning tailored as appropriate. Medical history (including medication use) and social history (including occupation) should also be explored. Examination should ideally include 3-pass nasoendoscopy rather than anterior rhinoscopy alone because nasoendoscopy affords views of the olfactory cleft. In addition to general endoscopic anatomy and structural abnormalities (such as septal deviation), signs of acute or chronic rhinosinusitis should be noted using a validated scoring system such as that proposed by Lund and Kennedy.[8] The visibility and patency of the olfactory cleft should be noted along with any abnormalities of this area (including discharge, polyps, edema, crusting, and scarring), ideally with a validated system such as the Olfactory Cleft Endoscopy Scale.[9] The presence of mass lesions should prompt full examination of the mucosal surfaces of the head and neck and further investigation as appropriate. The use of intranasal decongestant may aid endoscopic examination, although topical anesthetics should be avoided until after olfactory testing because these may cause temporary functional impairment. When a neurological cause of olfactory dysfunction is suspected, a full neurological examination should be performed, although detailed tests of cognition and memory should be undertaken by the appropriate specialists.

Recommendations can be summarized as follows:

- A full clinical history and examination should be undertaken, with 3-pass nasoendoscopy when possible.
- Local anesthetic should be avoided before olfactory testing.
- Where possible, findings should be presented in the context of validated clinical scoring systems.

Olfactory Assessment

The way in which olfactory function is tested is crucially important for accurate diagnosis and monitoring of impairment as well as

Table 1. Psychophysical Tests Used in Clinical or Research Work[a]

Psychophysical Test	Olfactory Components Assessed
Sniffin' Sticks	
Original version	Threshold, discrimination, and identification
Pediatric version	Identification (14-item)
Screening version	Identification (12-item)
Connecticut Chemosensory Clinical Research Center test	Threshold, identification
T & T Olfactometer (Daiichi Yakuhin Sangyo)	Threshold, identification
University of Pennsylvania Smell Identification Test	Identification
Smell diskettes test	Identification
Cross-Cultural Smell Identification Test	Identification
Pocket Smell Test	Identification
San Diego Odor Identification Test	Identification
Scandinavian Odor Identification Test	Identification
Smell threshold test	Threshold
Olfactory Perception Threshold Test	Threshold
Barcelona Smell Test	Odor detection, identification, and memory

[a] Adapted from Hummel et al.[13]

outcomes assessment. Broadly, olfactory testing can be divided into the following 4 categories:

1. Subjective assessment
2. Psychophysical olfactory assessment
3. Imaging
4. Electrophysiology

Subjective Assessment

Subjective assessment of olfactory function is necessary to determine the effects of impairment on patients and the effect of interventions. Such assessment can be performed using visual analog scales or Likert questionnaires or as part of a larger patient-reported outcomes measure. Although patient-reported outcome measures such as the Sino-Nasal Outcome Test and Rhinosinusitis Disability Index include specific questions on smell and taste, they are less able to differentiate between normosmia and hyposmia or anosmia than olfactory-specific, patient-reported outcomes measures such as the Questionnaire of Olfactory Disorders.[10] Furthermore, the Sino-Nasal Outcome Test and Rhinosinusitis Disability Index were validated for use in patients with CRS, preventing their use in patients with PIOD, for example. If a validated questionnaire is not available for the patient cohort in question, another recognized form of assessment, ideally quantitative and/or anchored, such as a visual analog scale, should be used.

Where patient-reported outcomes measures are used in the longitudinal assessment of function over time, such as to determine the effect of treatment, any change in score should be interpreted in the context of the minimal clinically important difference. The minimal clinically important difference is the smallest change in an outcome that would be deemed important to the patient or for their management. For the Questionnaire of Olfactory Disorders, the minimal clinically important difference is 5.2 points.[11]

Although establishing subjective experience is important, studies have demonstrated poor levels of correlation between subjective function and psychophysical test scores in healthy participants and patient populations.[5] From such studies, nasal patency can be confused with olfactory function, and dysfunction of gradual onset may go unnoticed.

In a cohort of 83 healthy study participants, Landis and colleagues[12] demonstrated that subjective ratings of olfactory function correlate significantly with measures of nasal patency when reporting occurred before psychophysical olfactory testing. When reporting occurred after psychophysical testing, the significant correlation between patency and subjective olfaction disappeared; instead, subjective ratings of olfactory function now correlated significantly with psychophysical test scores. From this work,[12] some form of training appears to be important in helping otherwise naive participants to assess their own olfactory function. In light of these findings, undertaking subjective olfactory assessment several times and then using the most recent scores or the mean of the scores obtained may be of benefit. However, to our knowledge, the utility of this approach has not yet been investigated.

Recommendations include the following:

- Subjective assessment should be undertaken using validated questionnaires where available. Where unavailable, anchored systems such as the visual analog scale should be used.
- Subjective assessment should not be performed in isolation but rather in conjunction with psychophysical testing.

Psychophysical Olfactory Assessment

Similar to an audiogram, psychophysical olfactory assessment involves presentation of an odor stimulus, with the test outcome depending on the participant's response. Such tests therefore require patients or participants to understand and cooperate with the health care professional or investigator. The tests can be used to evaluate orthonasal and retronasal olfaction as well as gustation, although different tests, with the appropriate odor or tastant stimuli, are required. Hummel et al[13] provide a discussion of retronasal and gustatory testing.

At present, several orthonasal psychophysical tests are available for clinical or research use (**Table 1**). Most commonly, these test odor threshold, the suprathreshold of odor discrimination and identification, or a combination of these. Odor threshold is the lowest concentration of an odorant that can be perceived by a participant; this threshold is therefore a test of quantitative olfactory function because perceived odor quality is not assessed. Odor discrimination is a form of suprathreshold test that assesses the participant's nonverbal ability to differentiate between stimuli of different quality. Odor identification is another common suprathreshold test that assesses the participant's ability to identify an odor correctly, usually through use of verbal or visual cues. Because suprathreshold tests use stimuli of sufficient strength to be perceived by participants with normosmia, odor discrimination and identification primarily aim to test qualitative olfactory function, although they also show a correlation with quantitative function.

Any psychophysical test used should be validated for the population in question, with diagnoses of impairment and improvement made in relation to age-matched, clinically anchored normative data. This validation is particularly important for odor identification because one's ability to identify an odor depends on prior learning, which is in turn influenced by culture and age. Testing in children may be possible using adult psychophysical tools depending on their ability to understand instructions and cooperate throughout the dura-

tion of the test. Where this is not possible, pediatric psychophysical tests can be used.

The use of multicomponent psychophysical testing (ie, combining ≥2 of odor threshold, discrimination, and identification) increases diagnostic sensitivity. For example, in a study of 2178 patients, the use of individual odor threshold (T), discrimination (D), or identification (I) scores to diagnose olfactory impairment was less sensitive than using composite TDI scores (64%, 56%, and 47% for T, D, and I, respectively). Sensitivity increased when pairs of subcomponents were used but still fell short of the composite TDI score.[14]

Recent evidence has also suggested that the pattern of subcomponent scores obtained in multicomponent tools may carry diagnostic information.[15] For example, odor threshold appears to be relatively unimpaired in central causes of olfactory dysfunction (such as focal cerebral excision) and correlates poorly with tests of cognition. Conversely, odor discrimination and identification correlate better with tests of cognition, and identification is known to be impaired in central olfactory dysfunction.[16,17] In line with this evidence, cross-sectional analysis of olfactory subcomponent test scores from 1226 patients with hyposmia showed that patients with sinonasal olfactory dysfunction had particularly impaired odor threshold scores, whereas those with Parkinson disease were particularly impaired in suprathreshold tasks.[15] Furthermore, multicomponent testing during longitudinal monitoring of patients may offer a benefit.[18]

The logistical effect of psychophysical testing should be considered during service planning. Tests such as the Sniffin' Sticks (Burghart) are administered by an investigator, and appropriately trained staff must therefore be available. Where such staff are unavailable, use of a self-administered tool, such as the University of Pennsylvania Smell Identification Test or the identification component of the Sniffin' Sticks, can be considered.

Recommendations include the following:

- Psychophysical tools should be reliable and validated for the cohort undergoing testing, with diagnoses of impairment and improvement made based on age-matched and clinically anchored normative data.
- Psychophysical assessment tools should include tests of odor threshold and/or a test of odor identification or discrimination. Use of multicomponent testing improves diagnostic sensitivity, and subtest pattern may aid the diagnosis of the underlying pathology.

Imaging

Magnetic resonance imaging scans of the brain and olfactory tract should be obtained when a high index of suspicion for intracranial pathology exists. In the case of PTOD, the pattern of lesions seen on imaging can be used to estimate the severity of olfactory dysfunction.[19] The diagnostic yield and cost-effectiveness of routine scanning in patients without a high index of suspicion for intracranial pathology is, however, debated.

When scanning is performed, diagnostic and prognostic information can be obtained through assessment of olfactory bulb volume and olfactory sulcus depth. Olfactory function is correlated with olfactory bulb volume, with hypoplasia or aplasia being more commonly seen in patients with impaired function. This finding has been shown for conditions such as PIOD, neurodegenerative diseases, and congenital olfactory dysfunction but is less clear in conditions such as sinonasal disease.[20-23] The cutoff volumes separating normal from hypoplastic olfactory bulbs were greater than 59 mm^3 for men and greater than 54 mm^3 for women 45 years or younger and greater than 52 mm^3 for men and greater than 43 mm^3 for women older than 45 years.[24] Olfactory sulcus depth has also been correlated with olfactory function.[25]

Structural differences in brain regions upstream of the olfactory bulb have also been demonstrated in patients with olfactory dysfunction.[5] For example, in patients with sinonasal disease, reduced gray matter volume can be demonstrated in olfactory-eloquent regions such as the medial orbitofrontal cortex and insula.[23] Moreover, improved olfactory function secondary to functional endoscopic sinus surgery is associated with gray matter volume increase in the olfactory bulb[26] as well as upstream olfactory brain regions.[27]

The use of functional imaging has helped to delineate olfactory-relevant brain regions and differences in central activity in varying conditions.[28] However, given that such scanning requires specialist equipment and knowledge, it is generally reserved for the research setting.

Inflammatory sinonasal disease should be imaged using computed tomographic scanning, which has the added advantage of delineating bony paranasal sinus anatomy. Although computed tomographic staging systems used in CRS correlate weakly with olfactory function, recent volumetric techniques have been proposed that specifically assess olfactory cleft opacification, which in turn may correlate better with olfactory function in some patients.[29]

Electrophysiology

Electrophysiological techniques can be used to assess olfactory function at the level of the neuroepithelium (electro-olfactography) or centrally (chemosensory electroencephalography). Both of these techniques require temporally precise delivery of odor stimuli and therefore necessitate an appropriate olfactometer, a device that delivers odorants of a set concentration at a set speed to a participant.[1] Given the cost and logistical issues surrounding olfactometer use, olfactory electrophysiology is generally limited to research or medicolegal settings.

Treatment

General

All patients with olfactory impairment should receive safety counselling. Smoke and gas alarms should be fitted and well maintained, and food should not be eaten past expiration dates. Patients with possible neurological causes of dysfunction or those experiencing mental health sequelae should receive appropriate referrals. When dysfunction is secondary to medication use, use of these medications should be changed or stopped, if possible.

Olfactory Training

In 2004, Wang and colleagues[30] showed that olfactory sensitivity for androstenone could be increased through repeated exposure to this odor. This principle has subsequently been applied in patients and healthy study participants, in whom improved olfactory function has been demonstrated after repeated and deliberate sniffing of a set of odorants during a period of at least 3 months (**Table 2**).[31-45] The most commonly studied regimen for such olfactory training involves 4 odors, one from each of the following categories: fruity, flowery, resinous, and spicy.

A recent meta-analysis[46] found significant positive effects of olfactory training on the individual subcomponents of odor thresh-

Table 2. Evidence for the Use of Olfactory Training After 2010[a]

Source	Study Type	Study Population	Results
Olfactory Training			
Al Aïn et al,[31] 2019	Prospective, controlled	Healthy participants (n = 12)	Intensive, modified OT results in improved olfactory function and increased cortical thickness in olfactory-eloquent regions
Hummel et al,[32] 2018	Prospective, controlled	Postinfectious olfactory loss, idiopathic smell loss (n = 23)	EOG responses more frequently obtained following OT
Langdon et al,[33] 2018	Prospective, controlled	Posttraumatic olfactory dysfunction (n = 21)	OT significantly improved odor threshold score but not BAST-24 score or subjective smell function
Oleszkiewicz et al,[34] 2017	Prospective, controlled	Postinfectious, idiopathic olfactory dysfunction (n = 108)	OT with odor mixtures or alternating odors does not significantly improve function compared with single-molecule odor training
Konstantinidis et al,[35] 2016	Prospective, controlled	Postinfectious olfactory loss (n = 111)	Short- (16 weeks) and long-term (56 weeks) training produced significantly improved olfactory function compared with control, with long-term significantly better than short-term
Negoias et al,[36] 2017	Prospective, controlled	Healthy participants	Unilateral OT produced significant increase in bilateral OB volume
Poletti et al,[37] 2017	Prospective	Postinfectious and posttraumatic olfactory loss (n = 96)	Training with light molecular-weight molecules produced significantly improved PEA threshold compared with heavy-weight molecules
Kollndorfer et al,[38] 2015	Prospective, controlled	Postinfectious anosmia (n = 7)	OT induced changes in functional connectivity evidenced with functional MRI
Altundag et al,[39] 2015	Prospective, controlled	Postinfectious olfactory loss (n = 85)	Longer OT with change of odor was effective for odor discrimination and identification
Mori et al,[40] 2015	Prospective, controlled	Healthy children (aged 9-15 y) (n = 72)	Improved threshold and identification in training compared with nontraining group
Damm et al,[41] 2014	Prospective, controlled	Postinfectious olfactory loss (n = 144)	OT was significantly more effective with high concentration of odors and dysfunction <12 mo
Geißler et al,[42] 2014	Prospective	Postinfectious olfactory loss (n = 39)	Longer duration (≥32 weeks) increased effectiveness of training
Konstantinidis et al,[43] 2013	Prospective, controlled	Posttraumatic and postinfectious olfactory loss (n = 119)	Significant improvement in both groups
Haehner et al,[44] 2013	Prospective, controlled	Patients with Parkinson disease (n = 70)	Significant increase in olfactory function
Fleiner et al,[45] 2012	Retrospective	Olfactory loss due to differing causes (n = 46)	Improvement of olfaction

Abbreviations: BAST-24, Barcelona Smell Test; EOG, electro-olfactogram; MRI, magnetic resonance imaging; OB, olfactory bulb; OT, olfactory training; PEA, phenyletheyl aclohol.

[a] Adapted from Hummel et al.[13]

old, discrimination, identification, and the composite TDI score. Thirteen studies were included, covering patients with postinfectious, posttraumatic, and idiopathic olfactory dysfunction. The authors found a large effect size for composite TDI score as well as identification and discrimination but small to moderate effect size for odor threshold. Furthermore, duration of olfactory training was significantly related to effectiveness, but only for odor identification and composite TDI score.[46] At present, further work is required to delineate the role of olfactory training in olfactory impairment secondary to sinonasal disease.

In addition to the evidenced improvement in olfactory function after olfactory training, this form of treatment carries very little risk of adverse effects, is cheap, and can be administered by the patient. For these collective reasons, olfactory training is an attractive treatment modality. Our recommendation includes olfactory training in treating patients with olfactory dysfunction of various etiology.

Medication

Olfactory dysfunction associated with CRS can be successfully treated with systemic and intranasal corticosteroids. Recent evidence has also suggested that CRS-related olfactory dysfunction improves after treatment with monoclonal antibodies, such as mepolizumab. These treatments have been covered extensively elsewhere and will therefore not be covered here.

The usefulness of corticosteroids in other causes of olfactory dysfunction is less well established than in CRS-related impairment, in part owing to lack of high-quality research. In view of this and the potential complications associated with corticosteroid use, such treatment is not recommended in non–CRS-related impairment.

The utility of phosphodiesterase inhibitors in the treatment of olfactory dysfunction is unclear. By preventing degradation of cyclic adenosine monophosphate (which is involved in the downstream olfactory receptor signaling cascade), such medications may enhance olfactory function. Several studies have shown promise in this respect. In 2009, significantly improved odor threshold scores were obtained after treatment of patients with pentoxifylline for nonolfactory complaints[47]; another study in the same year[48] demonstrated improved olfactory function after treatment with oral theophylline in a cohort of patients with hyposmia and reduced nasal and salivary levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate. However, other studies[49,50] (also Whitcroft K. L., unpublished data, 2019) have found no significant improvement in olfactory function after treatment with phosphodiesterase inhibitors, including sildenafil citrate, pentoxifylline, and caffeine. Furthermore, application of theophylline to rodent olfactory epithelium did not enhance electro-olfactography recordings.[51]

Some evidence suggests that intranasal calcium buffers such as sodium citrate may be of benefit in treating olfactory dysfunction. In theory, by reducing free intranasal calcium levels, this medication should reduce calcium-mediated feedback inhibition at the level of the olfactory receptor. Significantly improved odor identification scores have been demonstrated after one-off administration in patients with olfactory dysfunction of mixed causes[52] and in patients with PIOD.[53] A follow-up study in patients with PIOD further

demonstrated significantly improved composite odor threshold plus identification scores, again after one-off administration.[54] Further studies assessing the effect of sodium citrate following regular use are required.

Table 3 summarizes findings from studies addressing use of these and other medications.[52-66] Recommendations include the following:

- Limited evidence supports the use of corticosteroids for non–CRS-related olfactory dysfunction.
- Little evidence supports the use of phosphodiesterase inhibitors in olfactory dysfunction.
- The use of intranasal calcium buffers may be beneficial in treating PIOD but requires more research.

Surgery

Surgical treatment of sinonasal olfactory dysfunction is well established and should be undertaken in line with existing guidelines.[67] At present, little evidence is available for the efficacy of surgery in non–CRS-related olfactory dysfunction, in part owing to lack of high-quality, prospective studies. Where research does exist, results can be conflicting. For example, although some studies have documented improved olfaction after nasal septoplasty,[68] others[69] have found no significant improvement at 1 year after surgery. Septorhinoplasty may improve olfaction to a greater extent than septoplasty because of augmentation of the internal nasal valve.[70] Further research in this area is required.

Table 4 summarizes studies assessing the effect of surgery on non–CRS-related olfactory dysfunction.[69-75] Recommendations include further research to delineate the role of surgical intervention for non–CRS-related olfactory dysfunction.

Conclusions

Olfactory dysfunction is common and can have a significant effect on quality of life. For patients to receive accurate and reliable diagnosis and monitoring, we suggest assessment as outlined in this review. In particular, psychophysical testing should be performed in addition to subjective assessment. Olfactory training is beneficial in various subtypes of impairment and is therefore recommended. Further high-quality research is needed to develop and validate medical and surgical interventions for impaired olfaction.

Table 3. Abbreviated Summary of Evidence for Medications After 2010[a]

Source	Study Type	Treatment Method	Study Population	Results
Medication				
Hummel et al,[55] 2017	Retrospective	Intranasal vitamin A	Patients with postinfectious or posttraumatic dysfunction (n = 170)	Greater improvement in group receiving vitamin A plus olfactory training than olfactory training alone
Whitcroft et al,[54] 2017	Prospective, controlled	Intranasal sodium citrate	Patients with postinfectious olfactory loss (n = 49)	Significant improvement in composite threshold and identification scores after treatment compared with placebo
Whitcroft et al,[53] 2016	Prospective, controlled	Intranasal sodium citrate	Patients with olfactory loss of mixed causes (n = 57)	Significant improvement in postinfectious group
Jiang et al,[56] 2015	Prospective, controlled	Zinc and corticosteroid	Posttraumatic anosmia (n = 145)	Zinc and corticosteroid application showed significant improvement compared with no treatment; no difference in effectiveness between zinc and corticosteroid
Tian et al,[57] 2015	Experimental	Dexamethasone injection	Laboratory mice	Expression of genes in olfactory mucosa positively affected by glucocorticoids
Haehner et al,[58] 2015	Cross-sectional, controlled	Rasagiline	Patients with Parkinson disease (n = 224)	Rasagiline-treated patients presented with significantly better odor discrimination when Parkinson disease duration was <8 y
Schöpf et al,[59] 2015	Prospective, controlled	Intranasal insulin	Patients with postinfectious olfactory loss (n = 10)	Immediate (short-term) improvement of olfaction in 2 of 10 participants
Haehner et al,[60] 2013	Prospective, controlled	Rasagiline	Patients with Parkinson disease (n = 34)	No significant improvement
Schriever et al,[61] 2012	Retrospective	Systemic methylprednisolone	All causes among patients with olfactory dysfunction (n = 425)	Best improvement in patients with sinonasal disease, but also with other causes
Lyckholm et al,[62] 2012	Prospective, controlled	Oral zinc	Chemotherapy-related olfactory disorders (n = 58)	No improvement in olfactory loss
Reden et al,[63] 2012	Prospective, controlled	Vitamin A	Patients with postinfectious and posttraumatic olfactory loss (n = 52)	No significant effect
Henkin et al,[64] 2012	Prospective	Topical and systemic administration of theophylline	Patients with viral illness, allergic rhinitis, head trauma, congenital hyposmia, and other chronic disease processes (n = 10)	Oral theophylline treatment improved taste and smell acuity in 6 of 10 after 2-12 mo; intranasal theophylline treatment improved taste and smell acuity in 8 of 10 after 4 wk
Reden et al,[65] 2011	Prospective, controlled	Minocycline	Patients with postinfectious olfactory loss (n = 55)	No significant effect
Jiang et al,[66] 2010	Prospective	Oral high-dose corticosteroids	Posttraumatic anosmia (n = 116)	Improvement in some patients; possibly spontaneous recovery
Panagiotopoulos et al,[52] 2005	Prospective	Sodium citrate buffer solution to the nasal cleft	Patients with unspecified olfactory loss (n = 5), head trauma (n = 1), nasal surgery (n = 7), and post infection (n = 18) (n = 31)	Measured improvement in 97% of patients with 1 h; 74% noticed improvement

[a] Adapted from Hummel et al.[13]

Table 4. Evidence for Surgical Treatment of non–CRS-Related Olfactory Dysfunction After 2010[a]

Source	Study Type	Treatment Method	Study Population	Results
Surgery				
Morrissey et al,[71] 2016	Retrospective	Surgical resection of olfactory neuroepithelium	Patients with peripheral phantosmia (n = 3)	Resolution of phantosmia
Hanci et al,[72] 2016	Prospective	Laparoscopic sleeve gastrectomy	Morbidly obese patients with olfactory disorder (n = 54)	Improvement of olfaction after surgery
Randhawa et al,[70] 2016	Prospective	Functional septorhinoplasty	All patients listed for functional septorhinoplasty (n = 43)	Statistically significant improvement in screening odor identification scores but no proven clinical benefit
Altun and Hanci,[73] 2015	Prospective	Nasal septal perforation repair	Patients with septal perforation and olfactory disorder (n = 42)	Improvement in olfaction with successful closure of defect; closure success in 92.8%
Razmpa et al,[74] 2013	Prospective	Aesthetic septorhinoplasty	Patients with normal olfaction and no nasal functional abnormalities (n = 102)	No significant change in odor identification scores postoperatively
Schriever et al,[69] 2013	Prospective	Septoplasty with or without reduction of turbinates	All patients listed for nasal septal/turbinate surgery (n = 44)	No significant improvement in olfactory function at 3.5 mo
Richardson et al,[75] 2012	Prospective	Gastric bypass surgery	Morbidly obese patients (n = 55)	Patients with gastric bypass were more likely to have olfactory dysfunction preoperatively than controls, but function was not affected by surgery

Abbreviation: CRS, chronic rhinosinusitis.

[a] Adapted from Hummel et al.[13]

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