Olfactory and gustatory disorders

AWMF Guideline 0 17/0 50

Published by the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNO-KHC)

Other participating scientific societies and associations (alphabetical): German Professional Association of Otolaryngologists
German Society for Occupational and Environmental Medicine (DGAUM)
German Society for Otorhinolaryngology, Head- and Otolaryngology, Head and Neck Surgery (lead, DGHNO-KHC)
German Society for Pediatrics and Adolescent Medicine (DGKJ)
German Society for Neurosurgery (DGNC) German Society for Neurology (DGN)
German Society for Neuroradiology (DGNR)
German Radiological Society, Society for Medical Radiology (DRG)

Michael Damm 1, Thomas Hummel 2, Antje Hähner 3, Christian A. Müller 4, Önder Göktas 5, Boris A. Stuck 6, Antje Welge-Lüssen 7, Stefan Isenmann 8, Julia Vent 9, Thomas Kraus 10, Monika Probst 11, Markus Blankenburg 12, Sönke Langner 13, Barbara Carl 14

The guideline was approved by the boards of the participating professional societies / organizations on 01.08.2023.

Composition of the guideline group and authors of the DGHNO-KHC

1 Prof. Dr. med. Michael Damm (Line Coordinator), ENT Private Practice Cologne

2 Prof. Dr. med. Thomas Hummel (Deputy Head Coordinator), University Hospital Dresden / Medical Faculty TU Dresden

3 Prof. Dr. med. Antje Hähner, University Hospital Dresden / Medical Faculty TU Dresden

Assoc. Prof. PD Dr. Christian A. Müller, ENT Clinic, Medical University of Vienna;

5 Prof. Dr. med. Önder Göktas, ENT Center at Kudamm Berlin;

6 Univ.-Prof. Dr. med. Boris A. Stuck, Department of Otolaryngology, Head and Neck Surgery, Marburg University Hospital

7 Prof. Dr. med. Antje Welge-Lüssen, ENT Clinic Basel/Practice Rheinfelden

Representatives of the participating professional societies and associations

8 Univ.-Prof. Dr. med. Stefan Isenmann (mandate holder DGN), Clinic for Neurology and Clinical Neurophysiology at St. Josef Hospital Moers

9 Professor Dr. Dr. Julia Vent (mandate holder German Professional Association of Ear, Nose and Throat Physicians e.V.), practice owner, Cologne

10 Univ.-Prof. Dr. med. Thomas Kraus (mandate holder DGAUM), Institute for Occupational, Social and Environmental Medicine, RTWH Aachen

11 PD Dr. med. Monika Probst (DGNR mandate holder), Department of Diagnostic and Interventional Neuroradiology Klinikum rechts der Isar Technische Universität München

12 Prof. Dr. Markus Blankenburg (DGKJ mandate holder), Pediatrics, Stuttgart Hospital

13 Prof. Dr. med. Sönke Langner (DRG mandate holder), Radiological Group Practice Greifswald-Wolgast-Anklam, Greifswald

14 Prof. Dr. med. Barbara Carl (DGNC mandate holder), Clinic for Neurosurgery, Helios Dr. Horst Schmidt Kliniken Wiesbaden

Background, objectives and containment

The aim of this guideline is to provide physicians in clinics and practices with a systematically developed aid for decision-making in the care of patients with olfactory and gustatory disorders. The guideline is primarily aimed at ENT specialists, but also at neurologists, neurosurgeons, specialists in pediatrics and adolescent medicine, occupational and environmental physicians, and serves as information for general practitioners, family doctors, and internists.

Due to the clinically frequent overlap between olfactory and gustatory disorders, the treatment in a guideline seems reasonable (Landis et al., 2009, Landis et al., 2010c).

The focus of the guideline is on the medical field. The definitions and classifications proposed here have been derived from epidemiological and pathophysiological bases and are intended to complement or specify the systematics mentioned in the ICD code in section "R43." are intended to supplement or specify the systematics mentioned in the ICD code in the section "R43." for everyday clinical use.

The recommendations for diagnosis and therapy in this guideline are based on scientific principles, which on the one hand aim at quality assurance, and on the other hand reduce or avoid overdiagnosis, overtreatment, or the use of non-evidence-based procedures (Damm et al., 2004). This should improve the treatment for the benefit of the patients concerned. Due to the complexity of this objective, the former algorithms in the AWMF guidelines on olfactory and gustatory disorders are no longer applicable.

However, the causes of olfactory and gustatory disorders show a great heterogeneity, they often manifest as symptoms of different underlying diseases (Damm 2007, Deems et al., 1991, Haehner et al., 2013, Hummel and Welge-Luessen, 2009b, Landis et al., 2006, Reden et al., 2006a, Welge-Lüssen et al., 2009). For the majority of the underlying diseases, evidence-based recommendations for diagnosis and therapy are already available through guidelines or position papers. For the aforementioned case, the guideline Olfactory and Tasting Disorders refers to the already existing recommendations. On the other hand, the study situation remains unsatisfactory for many causes of olfactory and gustatory disorders, so that no or only insufficient experimental scientific evidence is available. In order to formulate the recommendations, an extensive analysis and

Assessment of the scientific literature. However, the analysis carried out here does not meet all the requirements for a complete systematic review of the available literature, not least due to the enormous breadth of content of the topic

"Olfactory and Tasting Disorders." Nevertheless, the recommendations are based on the current state of knowledge of the scientific literature and were made with the help of the many years of clinical experience of the members of the guideline group as an indication of a standard in diagnostics and treatment by expert consensus. The consensus of the recommendations was reached in a two-stage DELPHI process.

Consensus strength was classified by percent agreement as follows: Strong

consensus	> 95% of those eligible to vote
Consensus	> 75 - 95% of those entitled to vote
Majority approval	> 50 - 75% of those entitled to vote
no majority approval	< 50% of those entitled to vote"

In this consensus-based guideline (S2k), the adoption and determination of the strength of the recommendations was done through a formal consensus process, and a statement of schematic grades of recommendations or levels of evidence was not provided because there was no underlying systematic review of the evidence. The strength of a recommendation was expressed linguistically. The strength of recommendation was classified into the following categories:

Target - strong
recommendation Should -
recommendation
Can - open recommendation.

Gender-sensitive language

We use gender-sensitive language as much as possible in this guideline and have chosen to represent it using gender colons (:).

Table of contents

1 What's new ?

Since the last review, olfactory and gustatory disorders have been brought to public attention by the Corona pandemic. Also, our knowledge of monoclonal antibody therapy for chronic rhinosinusitis with nasal polyps has increased. Therefore, the current knowledge on SARS-CoV-2 associated olfactory and gustatory disorders and a chapter on therapeutic options with biologics with respect to sinunasal olfactory disorders have been added. All other chapters were also revised and the current state of knowledge from the new relevant literature was added.

In the definitions of quantitative classification of dysosmia or dysgeusia, the terms anosmia and "functional anosmia" or ageusia and "functional ageusia" should be used largely interchangeably.

2 Olfactory disorders (dysosmia)

2.1 Epidemiology

According to estimates by the National Institute of Health, there are 200,000 physician consultations for olfactory disorders in the USA each year (Panel on Communicative Disorders to the National Advisory Neurological and Communicative Disorders and Stroke Council, 1979). For German-speaking countries, an epidemiological study by Vennemann et al. (Vennemann et al., 2008) in 1277 participants showed that 3.6% of the general population had (functional) anosmia, 18% signs of hyposmia, and 20% signs of hypogeusia. These data are consistent with other national and international studies (Murphy et al., 2002, Brämerson et al., 2004, Landis et al., 2004, Schumm et al., 2009, Shu et al., 2009, Boesveldt et al., 2011, Pinto et al., 2014).

Based on a survey conducted in 2000 at all ENT clinics in German-speaking countries, it can be assumed that in Germany alone approximately 79,000 patients with olfactory disorders are treated in ENT clinics each year (Damm et al., 2004). The most frequent causes are sinunasal diseases (53% due to inflammations of the nose or paranasal sinuses, 19% due to respiratory disorders) with 72%. In the patient:inside collectives of ENT clinics, postviral olfactory disorders (11%) are found on the third frequency rank and in descending frequency followed by idiopathic olfactory disorders (6%), olfactory disorders after traumatic brain injury (5%), iatrogenic (3%),

toxic (2%) and congenital causes (1%). Non-sinunasal olfactory disorders together account for 28% of all olfactory disorders, although the proportion of these latter diagnostic groups is significantly higher in some centers (e.g., postviral olfactory disorders up to 91%) (Damm et al., 2004). According to a nearly identical, previously unpublished survey (Michael Damm, personal communication) from the fall of 2020, these values changed little overall - however, COVID-associated olfactory disorders were present in 6% of all those treated, bringing the proportion of postviral olfactory disorders to 18% (sinunasal causes 63%, postinfectious 12%, COVID-associated 6%;
traumatic 6%, idiopathic 5%, other 8%).

2.2 Terminology on quantitative and qualitative changes in olfaction.

The ICD code in section R43. "Disorder of sense of smell and taste" distinguishes only 3 diagnoses for olfactory disorders: R43.0 Anosmia; R 43.1 Parosmia; R 43.8 Other unspecified disorder of sense of smell and taste.

However, the aforementioned systematics should be supplemented or specified for clinical practice. Dysosmia is an umbrella term for qualitative **and** quantitative olfactory disorders. Quantitative disorders result from a reduction/abrogation or from an amplification (much rarer) of olfactory perceptions (cf. Table 1). Qualitative olfactory disorders are based on an altered, distorted or hallucinatory olfactory perception. (Table 2, overview in Hummel and Welge-Luessen, 2009b).

2.2.1 Quantitative classification of the smelling ability

Psychophysical tests of olfaction have been extensively standardized (Kobal et al., 2000, Hummel et al., 2007). As a result, data from larger subject and patient collectives are available, which allow the classification of olfactory ability into the categories normal olfactory ability (normosmia), reduced olfactory ability (hyposmia), and abolished olfactory ability (anosmia) (see (Kobal et al., 2000, Hummel et al., 2007, Oleszkiewicz et al. 2019). The terms "normosmia" and "hyposmia" are related to a group of healthy subjects aged between 21- 30 years. However, olfactory ability declines with increasing age (Hummel and Welge-Luessen, 2009b). Therefore, in the clinical evaluation of the individual

patients:inn addition, the expected olfactory ability of the corresponding age group should be considered even more specifically (Kobal et al., 2000, Hummel et al., 2007; Oleszkiewicz et al. 2019). The olfaction of the right and left sides of the nose is (largely) symmetrically expressed in most people. This is also true for dysosmia in quantitative olfactory disorders, only in about 25% of the patient:s significant side differences are found (Gudziol et al., 2007a, Welge-Lüssen et al., 2010).

In hyposmia, there is a limitation in the use of olfactory function in daily life.

Anosmia, on the other hand, describes a condition of severe restriction or abolition of olfactory perception in which meaningful use of the sense of smell in everyday life is no longer possible, even if a few odors can be noticed or perceived occasionally, faintly, or briefly, i.e., there is insignificant residual olfactory ability or complete abolition of olfactory ability.

Clinically, specific anosmia (synonyms: selective or partial anosmia) can be distinguished from anosmia. Specific anosmia is a markedly reduced sensitivity to a specific odorant/group of odorants with otherwise normal olfactory ability; specific anosmia has no pathological significance (Croy et al., 2015).

Hyperosmia, which is extremely rare clinically, is a measurable, quantitatively increased olfactory sensitivity, e.g., in migraine (Blau and Solomon, 1985).

Table 1 Overview of the quantitative classification of olfactory ability

Hyperosmia	Supernormal function (very rare)
Normosmia	Normal sensitivity
Hyposmia	Reduced sensitivity
Anosmia	Very significant impairment of olfaction, includes both complete loss and the presence of a small amount of residual perception ("functional anosmia"), whereby meaningful use of the sense of smell in everyday life is not possible.

2.2.3 Qualitative disorders of olfaction

A change in the perception of odors in the presence of an odor source is called parosmia (Hummel and Welge-Luessen, 2009b, Landis et al., 2010a). The perceptual changes may be pleasant or unpleasant; the term "cacosmia," which was often used in the past, should no longer be used. The site of origin is not precisely known; changes are thought to occur in the olfactory bulb or other central olfactory structures, but possibly also peripherally at the level of the olfactory epithelium (Bitter et al., 2011, Hummel and Welge-Luessen, 2009b, Landis et al., 2010a; Pellegrino et al., 2021). Because parosmia not infrequently occur weeks to months after damage to the olfactory system, they are sometimes interpreted as signs of olfactory regeneration or reorganization (Bitter et al., 2011, Croy et al., 2013, Hummel and Welge-Luessen, 2009b, Landis et al., 2010a; Liu et al., 2021).

Phantosmias are olfactory hallucinations, i.e., olfactory perception in the absence of a stimulus source. The origin in the olfactory system is largely unexplained (Hummel and Welge-Luessen, 2009b, Landis et al., 2010b), but dysfunction of, e.g., peripheral neurons or spontaneous activity at the level of the bulbus olfactorius or other central structures such as the amygdala is thought to be involved (Frasnelli et al., 2003; Holbrook et al., 2005; Hong et al., 2012).

Qualitative disorders of olfaction occur more frequently after infectious or traumatic damage to the olfactory system (Hummel and Welge-Luessen, 2009b, Landis et al., 2010b). A questionnaire is available to evaluate parosmias and phantosmias (Landis et al., 2010a). Quantitative tests to assess parosmias are under development (e.g., Liu et al., 2020, Sekine et al., 2022). Qualitative disorders of olfaction typically largely regress after months to years (Hummel and Welge-Luessen, 2009b, Landis et al., 2010b, Isenmann et al., 2021).

Olfactory intolerance is a subjective exaggerated sensitivity to fragrances with normal or even decreased olfactory sensitivity.

Table 2 Overview of qualitative changes in olfaction.

Parosmia	***Altered perception of*** odors ***in the presence of a stimulus source.***
Phantosmia	***Perception of*** odors ***in the absence of a stimulus source***
Olfactory Intolerance	***Exaggerated subjective sensitivity*** to fragrances ***in the case of normal or even reduced olfactory sensitivity***

2.2.4 Ortho- and retronasal olfactory function

Olfactory stimuli can be both orthonasal, i.e., via the nostrils, and retronasal,

i.e., via the oral cavity and the pharynx, reach the olfactory epithelium (Hummel and Welge-Luessen, 2009b). It is often observed that identical olfactory stimuli are perceived differently in ortho- or retronasal perception (Small et al., 2005).

In addition to the sense of taste, which provides us with information about the 5 tastes (sweet, sour, bitter, salty and umami), and the trigeminal nerve, which in addition to texture and temperature also conveys the pungency of food, the olfactory nerve is mainly responsible for perceiving the aroma of food. While in common parlance one speaks of the "taste" of food, in fact it is usually the smell that is meant.

With the orthonasal sense of smell, we perceive the outside world - fragrances enter the nasal cavity with the inhaled air via the nostrils and come into contact with the olfactory mucosa at the roof of the nose. In retronasal aroma perception, fragrances from food enter the nasal cavity from the oral cavity through the pharynx and then come into contact with the olfactory mucosa in the olfactory cleft.

Several studies have examined similarities of and differences between orthonasal and retronasal smelling. It has been found, for example, that olfactory thresholds are higher for retronasal than for orthonasal stimuli (Voirol and Daget, 1986) and that identification of retronasal stimuli is more difficult (Pierce and Halpern, 1996). Thus, there appear to be significant differences between ortho- and retronasal smelling.

This may be due to a variety of reasons, e.g., in the case of orthonasal olfaction, modulation of airflow through the nose or, for example, that odors elicit different activation patterns in the olfactory epithelium due to different chromatographic properties, which in turn causes different activation patterns in the olfactory bulb (Hummel et al., 2006; Scott et al., 2014; Mozell 1964). In addition, the

Olfactory sensations modulated by experience or physiological states, such as appetite or hunger (Kadohisa 2013).

2.3 Definition and cause-related classification of Olfactory disorders.

Based on the epidemiological data available today, it is useful to divide olfactory disorders into ***sinunasal*** and ***non-sinunasal*** disorders (Damm et al., 2004). In the case of ***non-sinunasal*** causes, primary sustained damage to the olfactory system (olfactory epithelium, olfactory pathway) is present in some cases.

2.3.1 Sinunasal dysosmia

Definition: *Sinunasal olfactory disorders summarize as an umbrella term dysosmias whose causes arise from etiologically different diseases or changes in the nose and/or paranasal sinuses. The olfactory system is affected as part of an underlying disease.*

Epidemiologically, inflammatory diseases such as chronic rhinosinusitis and polyposis nasi et sinuum are of greatest importance. To a lesser extent, olfactory disorders also occur in allergic rhinitis and so-called non-allergic/idiopathic rhinitis. Other causes in this group may include intranasal neoplasms (e.g., inverted papillomas, adenocarcinomas), posttraumatic conditions (e.g., stenoses), extreme surgical remodeling of the nasal airways (e.g. "Nasalization surgery"), the abolition of nasal breathing after total laryngectomy or drug side effects (e.g. due to mucosal swelling caused by hormone therapies) (reviews e.g. in Damm et al., 2004, Damm 2009, Hummel and Welge-Luessen, 2009b). For the most important causes (chronic rhinosinusitis, polyposis nasi et sinuum, allergic rhinitis), German and international guidelines or position papers exist that summarize the current state of knowledge on pathophysiology, diagnostics, and therapy in an evidence-based manner (Bousquet et al., 2008, Bousquet et al., 2012, Fokkens et al., 2012b, Stuck et al., 2012; Stuck et al., 2018; Fokkens et al., 2020).

Pathophysiologically, according to current knowledge, the restriction/elimination of olfactory function is often based on a negative influence of inflammatory changes (e.g., interaction with inflammatory cytokines or cells) on the function of the olfactory epithelium and/or on conductive processes (e.g.

mechanical blockage of odorant transport to the olfactory cleft due to nasal polyps or extreme septal deviations). The initially mostly reversible functional limitations of olfaction may turn into permanent limitations or loss of olfaction, especially in the case of long-term inflammation, due to progressive destruction or remodeling of the olfactory epithelium (e.g., in the context of "airway remodeling") (Bousquet et al., 2008, Bousquet et al., 2012, Damm et al., 2004, Damm 2007, Damm 2009, Klimek et al., 1997a, Stuck et al., 2018 ; Bachert et al., 2020 ; Orlandi et al., 2016).

2.3.2 Non-sinunasal dysosmia

2.3.2.1 Post-infectious olfactory disorders

Definition: *Postinfectious olfactory dysfunction is a persistent dysosmia following a temporary infection of the (upper) respiratory tract without a symptomless interval between the end of the infection and the observation of the olfactory dysfunction. This is to be distinguished from olfactory dysfunction in the context of a respiratory tract infection, in which olfaction normalizes after the infection has healed and the conductive/inflammatory causes have receded (Hummel et al., 1998).*

Postinfectious olfactory disorders are one of the most common causes of non-sinunasal olfactory disorders (Damm et al., 2004, Deems et al., 1991, Seiden 2004). They are not infrequently accompanied by parosmias or phantosmias of various degrees, which are reported by a large number of the patient:s (Damm et al., 2013, Duncan et al., 1995b, Landis et al., 2010a, Landis et al., 2010b; Doty 2022; Pellegrino et al. 2021; Ohla et al. 2022).

In addition to coronaviruses (Doty 2022), rhinoviruses, among others, are discussed as the triggering agent of postinfectious olfactory disorders (Suzuki et al., 2007). According to studies, the frequency peak of the diseases in spring and early summer suggests the involvement of influenza and parainfluenza (type 3) viruses after comparing epidemiological data, comparing symptoms of the disease and determining antibody titers (Konstantinidis et al., 2006). Detection and identification of the viruses are difficult because many patient:s consult a physician late (Hendriks 1988). There seems to be no correlation between the clinical severity of the viral infection and the occurrence of postviral olfactory dysfunction (Bednár M. 1930).

Etiologically, different causal pathomechanisms are discussed (e.g., viral toxins, involvement of bacteria, autoimmune reaction against the olfactory epithelium, lack of receptor expression) (Hummel and Welge-Luessen, 2009b, Landis et al., 2005; Zazhytska et al., 2022). Olfactory loss is probably predominantly caused by direct damage to the olfactory mucosa (Jafek et al., 1997, Jafek et al., 2002) and in SARS-CoV-2 is brought about by attack of the sustentacular cells ("sustentacular cells"; Khan et al., 2021), which may indirectly lead to temporary or permanent loss of function (Isenmann et al., 2021). Histopathological studies of biopsies of the olfactory mucosa have demonstrated scarred regions in patients:with postinfectious olfactory loss, where the olfactory epithelium has been replaced by respiratory epithelium (Jafek et al., 2002; Khan et al. 2021). The observed reduction in olfactory receptor neurons correlates with the extent of olfactory dysfunction (Jafek et al., 1997, Jafek et al., 2002). In hyposmia, a smaller reduction in the number of olfactory receptor neurons was observed in biopsies of the olfactory cleft compared with anosmic subjects (Jafek et al., 2002). The above observations are also consistent with the results of previous studies describing a reduction in the thickness of the olfactory epithelium and a decrease in the number of receptor neurons and nerve fibers, respectively, in postinfectious olfactory dysfunction (Yamagishi M et al., 1994). In addition, irregular nuclei, replacement of olfactory epithelium by metaplastic squamous epithelium, fibrosis, and a decrease in the number of Bowman's mucous glands have been described (Henkin et al., 1975, Seiden 2004, Yamagishi M et al., 1994, Yamagishi et al., 1992). In addition to direct damage to the nasal olfactory epithelium, central olfactory structures may also be affected (Rombaux et al., 2006; Isenmann et al., 2021).

2.3.2.2 **Posttraumatic olfactory disorders**

Definition: *Posttraumatic olfactory dysfunction is a loss of olfactory ability in connection with a head trauma, whereby a temporal connection to the trauma must be given (maximum six* months*; in case of a longer latency, an individual decision must be* made*).*

In this context, olfactory dysfunction after trauma may be due to an avulsion of the fila olfactoria (Delank and Fechner, 1996), but probably also to contusions of olfactory significant brain areas (e.g., in the orbitofrontal cortex or the bulbus

olfactorius (Lötsch et al., 2015, Lötsch et al., 2016, Schofield et al., 2014). In approximately 10-35% of patients with post-traumatic olfactory disorders, olfaction may partially return (Sumner, 1964; Reden et al., 2006).

In posttraumatic anosmia, complete spontaneous remissions do occur years after olfactory loss, but these are rare. Prognostically favorable factors with regard to recovery after posttraumatic olfactory loss are considered to be, if possible, a high level of residual olfactory capacity, female gender, youthful age, nonsmoker, initial parosmia, no lateral differences in olfactory function, and possible large amplitudes of event-related potentials to trigeminal or olfactory stimuli, as well as the size of the olfactory bulb (Hummel and Welge-Luessen, 2009b, Schofield et al., 2014). The time elapsed since the onset of olfactory dysfunction is also prognostically significant,

i.e., the longer the olfactory disorder persists, the lower the likelihood of remission (Reden et al., 2006; Rombaux et al., 2012).

2.3.2.3 **Toxic-induced olfactory disorders**

Definition: *Toxic olfactory disorders are defined as peripheral or central damage to the olfactory system caused by acute or chronic exposure to noxious substances.*

Olfactory disorders can occur in association with exposure to numerous drugs, toxins, as well as workplace and environmental influences (Amoore, 1986, Gobba 2003), including antibiotics (e.g., streptomycin), antirheumatic drugs (e.g., D-penicillamine), antihypertensive drugs (e.g.E.g., diltiazem, nifedipine), antidepressants (e.g., amitriptyline), chemotherapeutic agents (e.g., methotrexate), psychotropic drugs (e.g., amphetamines), sympathomimetics (e.g., chronic use of local vasoconstrictive agents) (Knecht et al. 1999), manganese (Bowler et al., 2011), solvents (Genter and Doty, 2019), alcohol, or cigarette smoke (Frye et al., 1990, Vent et al., Am J Rhinol. 2003). Improvements can be observed after removal of noxious agents or discontinuation of medication, e.g., after cessation of chemotherapy (Steinbach et al., 2009). On the other hand, irreversible damage can also occur, e.g., due to acids that have destroyed the basal layer of the olfactory mucosa. If there is a reasonable suspicion of occupational causation or contributory causation of an olfactory disorder, a suspicion report must be sent to the responsible statutory accident insurance or the responsible industrial physician in accordance with § 202 SGB VII. Patients must be informed by the notifying physician of the suspicious report.

consent is not required (however, this does not apply to notifications pursuant to Section 9 (2) SGB VII).

2.3.2.4 Congenital olfactory disorders

Definition: *"Congenital" or "congenital" are* olfactory *disorders that persist throughout life and for which the history and examination findings do not reveal any acquired causes (especially sinunasal diseases, relevant trauma, postinfectious olfactory disorders).*

Typically, there is little distress in "congenital" olfactory dysfunction. Using imaging techniques (MRI), hypo- or aplasia of the olfactory bulb may be present or flattening of the olfactory sulcus (Abolmaali et al., 2008). However, cases with present olfaction in the absence of bulbus olfactorius have also been described (Weiss et al., 2019). Isolated congenital anosmia is the most common; estimates suggest a frequency of approximately 1:8000 (Abolmaali et al., 2008). Other forms of congenital anosmia, such as Kallmann syndrome (hypogonadotropic hypogonadism associated with olfactory impairment), require early workup of the condition in collaboration with pediatrics or endocrinology (Karstensen and Tommerup, 2012). Other syndromal forms of congenital anosmia are found in Bardet-Biedl syndrome, Refsum syndrome, Usher syndrome, or congenital pain sensitivity in sodium voltage-gated channel alpha subunit 9 **(**SCN9A) mutation (Hummel and Welge-Luessen, 2009b).

2.3.2.5 Olfactory disorders in the context of non-sinunasal underlying diseases

Definition: *olfactory disorders that have a clear relationship to a neurologic, psychiatric, or internal disease.*

Olfactory disorders are a frequent accompanying symptom of neurological diseases, with neurodegenerative diseases in particular being associated with olfactory disorders. They are found in more than 90% of patients with idiopathic Parkinson's disease (Haehner et al., 2009) and are considered a supportive diagnostic criterion in clinical diagnosis (Postuma et al., 2015). In this context, the majority of

patients already have a pronounced hyposmia or anosmia at the time of diagnosis, which in rare cases may be accompanied by parosmia or phantosmia. Currently, olfactory disorders are thought to precede motor symptoms, sometimes by more than ten years (Haehner et al., 2019; Roos et al., 2022). Therefore, at least in some patients with idiopathic olfactory loss, an incipient idiopathic Parkinson's syndrome must be considered and neurologically clarified (Haehner et al., 2019); this is even more likely if other non-motor symptoms such as sleep disturbances and a depressive symptomatology as well as a positive family history of IPS are present (Berg et al., 2013; Haehner et al., 2019). Atypical parkinsonian syndromes are less commonly associated with olfactory disorders. In multisystem atrophy, olfactory dysfunction occurs to a lesser extent, whereas patient:ing with progressive supranuclear palsy and corticobasal degeneration show only mild impairment. Patients with restless legs syndrome and essential tremor show almost unrestricted olfaction (Hummel and Welge-Luessen, 2009b, Krismer et al., 2017).

Severe olfactory dysfunction is also found in Lewy body dementia, frontotemporal dementia, and Alzheimer's dementia (Doty and Hawkes, 2019). Olfactory dysfunction is also an early symptom of Alzheimer's disease and can be detected in patients with mild cognitive impairment, with limitations in odor identification being a powerful predictor of conversion to dementia (Conti et al., 2013).

Huntington's disease is associated with moderate hyposmia (Nordin et al. 1995). Patient:s with spinocerebellar ataxia and with Friedreich's ataxia show mild to moderate olfactory dysfunction (Doty and Hawkes, 2019). Olfactory dysfunction is also observed in motor neuron disease (Doty and Hawkes, 2019) and in patients with myasthenia gravis (Leon-Sarmiento et al., 2013).

In neurology, olfactory disorders are also found in 20-45% of patients with multiple sclerosis (Lucassen et al., 2016; Printza et al., 2022) and in temporal lobe epilepsy, especially in the seizures with unpleasant olfactory hallucinations (which most likely justified the previously used term "cacosmia") (Kohler et al. 2001). In psychiatry, olfactory disturbances occur in the frequent affective disorders, especially in patients with an acute

depressive episode (Negoias et al., 2010) and in schizophrenia patients (Moberg et al., 2014).

In addition to neurological causes of olfactory disorders, numerous internally caused olfactory disorders can be found, e.g., in connection with complicated diabetes mellitus type II (Naka et al. 2010), kidney diseases (Frasnelli et al., 2002), liver diseases (Temmel et al., 2005), or sleep apnea (Siegel et al., 2021). - appropriate specialist diagnostics would be advisable to confirm the underlying disease.

Table 3 Expression of olfactory disorders in neurological diseases.

Smell loss (characteristic expression)	**Disease**	**Special features**
Slightly (Norm- to Hyposmia)		
easy	Atypical Parkinson's syndromes: multisystem atrophy Progressive supranuclear ophthalmoplegia Corticobasal degeneration	
none to moderate	Multiple sclerosis	
light to moderate	Mild cognitive impairment	Identification deficit predictive of conversion to dementia
light to moderate	Temporal lobe epilepsy	Limitations especially in identification and discrimination
Moderate (hyposmia)		
	Motor neuron diseases (amyotrophic lateral sclerosis)	
	Myasthenia gravis	
	Huntington's disease	
Pronounced (marked hyposmia or anosmia)		
	Idiopathic Parkinson's syndrome	Typical early symptom, often not noticed by patients
	Alzheimer's dementia, Lewy body dementia, frontotemporal dementia	Typical early symptom in Alzheimer's dementia
Very variable		
Normosmia to anosmia	Familial Parkinson's syndromes (e.g. mutations at the gene loci leucine-rich repeat serine/threonine kinase2 (LRRK2) or phosphatase and tensin homolog induced kinase-1 (PINK-1).	Different expression in individual gene loci

2.3.2.6 Idiopathic olfactory disorders

Definition: *This refers to olfactory disorders that occur without an identifiable cause and cannot be assigned to any of the above categories.*

Consequently, "Idiopathic olfactory dysfunction" is a diagnosis of exclusion that requires a very thorough history and a comprehensive diagnostic workup, possibly at multiple time points.

2.4 Basic diagnostics for olfactory disorders

Basic diagnostics include a general and specific history (triggering events, temporal development, concomitant symptoms, relevant diseases / surgeries / medications / noxious agents), an ENT status, endoscopy of the nose / nasopharynx including an evaluation of the olfactory cleft, olfactory testing with a validated test procedure, and screening of the global smack function (cf. 2.6.1.1 (Hummel et al., 2001, Hummel et al., 2007; Welge-Luessen et al., 2013)).

2.5 Investigative procedures for olfactory disorders

According to a survey of German ENT clinics in 2010/2011, various methods are used for diagnosis, with the Sniffin' Sticks test being performed most frequently (91%). In Germany, other test procedures used are the Börnstein smell test (13%), the squeeze-bottle test (5%), and the University of Pennsylvania Smell Identification Test (UPSIT, 1%) (unpublished data, Damm 2016). The Sniffin' Sticks Test was developed for the German-speaking region and is also already preferentially used in clinical and scientific investigations in this area (July 2022: 415 publications in Medline in the search:
"'Sniffin' Sticks' (Austria or Germany or Switzerland)"; in contrast, only 18 hits in the search: "UPSIT (Austria or Germany or Switzerland)"). In German-speaking neurology, too, the Sniffin' Sticks Test is preferably used in the context of early detection and discrimination of idiopathic parkinsonian syndrome (Krismer et al., 2017). The present presentation therefore focuses on the test procedures used today in practice and in studies. For the assessment of the reliability of the psychophysical test procedures commonly used today for the diagnosis of olfactory disorders, the following are available

correlation coefficients are available. However, these alone are not sufficient to prove equivalence (agreement) (Bland et al., 1986, Grouven et al., 2007); equivalence tests are lacking in the older literature but are typically shown with newly introduced olfactory tests (Sorokowska et al., 2015; Nakanishi et al. 2022).

2.5.1 Psychophysical testing of the orthonasal olfactory function

2.5.1.1 Screening of the olfactory function (validated methods)

Screening procedures can in principle be used to exclude anosmia (Gudziol and Förster, 2002). There are a number of different procedures, usually based on the identification of odors (historical overview in Wenzel, 1948). All test procedures presented in the following have been validated.

(1) With the smelling sticks "Sniffin' Sticks" a screening of the olfactory function is possible. For this purpose, either the 16 sticks can be used, which are also found in the so-called "extended test" (Kobal, 2000, Hummel et al., 2007) or the application of an identification test based on 12 odorants (Hummel et al., 2001). It is reusable and can be performed by patients themselves (Mueller et al., 2006). The retest reliability is r=0.73 (Hummel et al., 1997) for the 16-scent test and r=0.78 (Hummel et al., 2001) for the 12-scent test.

(2) The CCSIT (Cross-Cultural Smell Identification Test) is an olfactory function screening test in which 12 odorants are microencapsulated on paper and released by rubbing with a pen (Doty et al., 1996). The different odorants in this test must be identified using a list of 4 terms each. The test has a long shelf life and is very well validated. It can also be performed by the patients themselves. A disadvantage is that the terms and fragrances used are adapted to the US language area. The retest reliability is r=0.71 (Doty et al., 1996).

(3) The Zurich Olfactory Test (Simmen et al., 1999, Simmen and Briner, 2006) is based on the presentation of odors in 8 so-called "olfactory disks", each of which must be identified on the basis of a selection of 3 terms. The test is reusable and can be administered by patients themselves. The retest reliability is not known.

Other, very simple test procedures such as the "alcohol sniff test" (Davidson and Murphy, 1997), or the "pocket smell test" (Duff et al., 2002) will not be discussed in more detail here (overview in (Drews and Hummel, 2016)). In 2021 and 2022, a number of novel olfactory tests were also published as a result of the SARS-CoV2 pandemic, although their value remains to be demonstrated in practice (e.g., Nakanishi et al. 2022; Snitz et al. 2022; Weir et al. 2022; Parma et al. 2021; Sekine et al. 2022; Hunter et al. 2023).

2.5.1.2 **Quantitative, validated methods for the study of olfactory function.**

In recent years, standardized tests for the quantitative, psychophysical examination of olfactory disorders have been developed and validated. These tests allow a detailed assessment of olfaction in terms of anosmia, hyposmia or normosmia. The use of these procedures is also useful for follow-up examinations.

These include

(1) the "Sniffin' Sticks" (Kobal, 2000, Hummel et al., 2007). Here, fragrances are packaged in felt-tip pens and released by removing the pen cap. Fragrance application occurs by holding the tip of the pen in front of the nasal entrance. The pens can be used for at least six months. The test includes odor identification and discrimination testing, as well as a threshold test that can be performed for butanol or phenylethyl alcohol (Croy et al., 2009; but see also Zernecke et al., 2011). Advantages of the test are the detection of different olfactory functions. Test-retest reliability (for a healthy group) was reported to be r=0.61 for the threshold test, r=0.54 for the discrimination test, and r=0.73 for the identification test (Hummel et al., 1997). For the extended version, the reliability (including patient:internal data) is reported as r=0.92 for the threshold test, r=0.80 for the discrimination test with 32 items, and r=0.88 for the identification test with 32 items (Haehner et al. 2009; Sorokowska et al. 2015). Interestingly, only for this test is there a publication in which the clinical significance of changes in the test score was explicitly investigated (Gudziol et al., 2006). Likewise, boundary conditions of test application have been thoroughly explored (e.g., Sorokowska et al., 2015b; Walliczek-Dworschak et al. 2016).

With the exception of the scent recognition test (Mueller et al., 2006), the test must be administered by an examiner. An advantage of the Sniffin' Sticks test is its repeated applicability, but a disadvantage is its limited shelf life. For an overview of olfactory tests from the "Sniffin' Sticks" family, see Walliczek et al. (Walliczek et al., 2016).

(2) the UPSIT (University of Pennsylvania Smell Identification Test), in which 40 odorants are microencapsulated on paper (Doty, 1995). These microcapsules can be opened mechanically by rubbing with a pen. The different fragrances must be identified in this test using a list of 4 terms each. The test has a long shelf life, is very well validated and widely used. For the most part, this test can also be performed by the patient him/herself; it is also available in international versions, although rarely validated specifically for individual countries. A disadvantage is that the test only examines the identification of odors. Test-retest reliability has been reported to be r=0.91 (Doty et al., 1984).

(3) the Connecticut Chemosensory Clinical Research Center (CCCRC) test according to Cain (Cain et al., 1988). This test is a combination of a sulfur test for butanol and an identification test for 10 odors. The odorants are provided in squeezable polypropylene bottles (sulfur test) and salt shaker-like glass bottles. An advantage is the detection of different olfactory functions, disadvantages are the comparatively poor validation, the performance of the threshold measurement in the model of ascending concentrations, and the small number of odorants used in the identification task (Hummel et al., 1997). The test cannot be performed by patients:themselves. It is not offered commercially, but can be easily made by the patient. The n-butanol threshold test (BTT) in the technique of the CCCRC test (Cain et al., 1983) has been frequently used in previous studies, but it is not a reliable test instrument according to Hummel et al. (Hummel et al., 1997). The BTT of the CCCRC test uses the principle of the so-called once ascending stimuli (MAL: method of ascending limits). The test substance butanol must be distinguished by the subject from distilled water offered in parallel; if this is not successful, the next stronger concentration is offered, and so on. (Cain et al., 1983). The olfactory threshold is considered to be determined as soon as the subject has given a series of four correct answers in succession.

The correlation between test and re-test was only r=0.36 (Hummel et al., 1997), so that a result obtained with the BTT can probably hardly be repeated. Thus, the significance of a supposedly significant difference between two treatments compared using the BTT must also be considered low, since it is questionable whether this result can be reproduced. The so-called procedure according to Murphy does not differ from the CCCRC test (Murphy et al., 1990).

Other psychophysical tests such as the "T&T Olfactometer" (a threshold and identification test for 5 odorants (Kondo et al., 1998)) commonly used in Japan or the Spanish odor identification test BAST-24 (Cardesin et al., 2006) will not be discussed here.

2.5.2 Psychophysical testing of the retronasal olfactory system

To test retronasal olfaction, validated procedures are available in the form of the so-called "tasting powders" (test-retest reliability of r=0.76) or the "candy smell test" (test-retest reliability of r=0.75), which are very easy to apply (Heilmann and Hummel, 2004, Renner et al., 2009, Haxel et al. 2011, Croy et al., 2014; Prem et al. 2022). Here, either scented powders (e.g., vanilla sugar, coffee powder, ground cinnamon, etc.) or sweet candies are placed in the mouth, which release scents when sucked or chewed. These retronasal olfactory sensations are then to be named using lists of verbal descriptors.

Indeed, there are patients with dissociation of ortho- and retronasal olfaction (Landis et al., 2003). Clinically, conditions are observed in which the orthonasal olfaction is extinguished, but the retronasal olfaction is still preserved, so that a check of the retronasal olfaction seems reasonable (Landis et al., 2005b, Gudziol et al., 2007).

2.5.3 Objective testing of the ability to smell

For the objectification of olfactory disorders, olfactory event-related potentials (OEKP) can be recorded (Kobal, 1981, Hummel et al., 2000). However, due to the equipment and time required, this method is only used in a few centers. The derivation of OEKP is clinically useful when psychophysical tests cannot accurately determine whether hyposmia or anosmia is present. Such cases may be considered, for example, in the examination of children, in cases of comprehension problems, or in cognitively impaired persons. Medical reports represent another indication; a position paper on the application and interpretation of test results exists for this purpose (Stuck et al., 2014).

2.5.4 Further examination options of the olfactory system

The performance of functional magnetic resonance imaging after olfactory activation (Kettenmann et al., 2001; Zang et al. 2021) and the derivation of electro- olfactograms (Lapid and Hummel, 2013) currently play no role in clinical routine. Other, indirect measurements to determine olfaction are performed only at specialized centers (Gudziol and Gramowski, 1987, Furukawa et al., 1988, Delank, 1998). The methods mentioned in this paragraph are generally reserved for scientific questions and currently play no role in patient:ing care.

Recommendation for the use of psychophysical testing procedures in olfactory disorders.

Due to its widespread use and high acceptance, psychophysical testing in German-speaking countries should preferably be performed with the Sniffin' Sticks test. Advantages are the availability of different test variants ("screening test", "SDI test") and of age-specific norm ranges from the German-speaking area. Alternatively and/or complementarily, other validated psychophysical procedures can be used for olfactory testing (e.g., tasting powder test, candy smell test). A disadvantage of most of the currently available psychophysical test procedures is the so far unsatisfactory statistical verification regarding test-retest reliability in the literature (e.g. by equivalence tests or Bland-Altman diagrams). Supplementary studies on test methodology appear necessary in the future.

(Strong consensus)

2.6 Therapy of Olfactory disorders

Patient counseling plays a central role in the treatment of dysosmia. In the daily routine, it is not uncommon for deficits to occur in medical consultations (Haxel et al. 2012; Landis et al. 2009; Philpott et al., 2021). These include, in particular, education about safety aspects: e.g., that leaked gas and fire smoke may not be detected or may be detected late, or that spoiled food may be inadequately detected. Likewise, the social and/or hygienic aspects should be addressed in a medical consultation (Haxel et al. 2012).

For the treatment of olfactory disorders, very different therapeutic measures are used in daily routine. Besides abstinence measures (e.g., noxious substances, medications), mainly conservative treatments are used (especially pharmacological therapies, olfactory training, acupuncture). Surgical measures are predominantly aimed at improving underlying sinunasal diseases (Damm et al., 2004).

Olfactory disorders may improve spontaneously. In the case of postinfectious dysosmia that has already existed for a longer period of time, data can be found in the literature, with approximately 15% of those affected achieving a significant improvement (not complete restitutio) after 6 months and approximately 30% after 12 months (Damm et al., 2013). The spontaneous remission rate seems to be similar for post-traumatic olfactory disorders in the first year after the accident, after

According to the literature, partial recovery occurs in 10 to 35% of cases (Reden et al., 2006a). In the delta variant of SARS-CoV 2 associated olfactory disorders, there is typically a complete loss of smell during the acute infection, which then improves after a short time in a majority of patients. Approximately 6 months after a corona-related infection, more than 80% of affected individuals report extensive recovery (Isenmann et al., 2021). The Omicron variant appears to cause significantly less olfactory disturbance (Boscolo-Rizzo et al., 2022).

Spontaneous (partial) recoveries may be based on a (recurrent) physiological regeneration of the olfactory epithelium or central olfactory structures on the one hand, and on an improvement of the triggering underlying disease on the other hand (for example, in sinunasal olfactory disorders due to a decrease in inflammation, Damm et al., 2013, Hummel and Welge-Luessen, 2009b). The background in corona-related olfactory loss lasting only days or weeks seems to be damage to the supporting cells in the olfactory mucosa (Brann et al., 2000). If the supporting cells recover, olfaction recovers. However, in the course of this infectious event, there is apparently also often a demise of olfactory receptor neurons, which can then be regenerated from basal cells (Khan et al., 2021).

Although detailed data on spontaneous remission rates in olfactory disorders of other causes are not yet available, spontaneous improvements can be assumed in many groups. Exceptions are progressive neurodegenerative diseases, especially M. Parkinson and M. Alzheimer. Due to the insufficient possibility of differentiation from natural healing processes, therapy results from uncontrolled studies (e.g. case reports, case series) can not or only insufficiently be evaluated with regard to their evidence. Therefore, data from uncontrolled studies were not considered in the therapy recommendations made here.

When olfactory dysfunction occurs in the context of underlying diseases in the ENT field, for which evidence-based recommendations are already available, reference was primarily made to the corresponding guidelines or position papers, since an improvement in dysosmia can often also be achieved via successful treatment of the underlying disease. In addition, a literature analysis (PubMed(R) , Cochrane Library(R) , standard textbooks, related guidelines) was performed to identify relevant publications on the topic of dysosmia.

"Therapy of olfactory disorders" was identified and then subjected to several filtering processes.

were evaluated. The evidence assessment took place according to the Oxford Center for Evidence-based Medicine (May 2001, revised Phillips et al., 2009) classification of evidence types for therapy studies, taking into account the considerations of study quality mentioned below. The literature review was directed toward conservative therapeutic approaches (specifically pharmacological therapy, olfactory training, acupuncture), and the primary English and German literature was included. Animal studies were not included due to the limited or questionable transferability of results from animal studies to humans, due to structural and anatomical differences in the olfactory system. Because of the insufficient delimitability of non-controlled studies (case reports, uncontrolled case series, evidence type IV) versus spontaneous remissions, this study design was mostly disregarded. Other important criteria for evaluating treatment effects in the literature include study quality and sample size. Study quality was assessed using the Jadad extended scale (Jadad et al., 1996). The significance of effect size is related to case size, so that with larger sample sizes, even smaller effects lead to rejection of the null hypothesis. With this in mind, case numbers were also examined in the studies analyzed here. The following considerations were taken into account in the assessment of study quality. If, for example, mean values are compared by means of a T-test, a sample size of 64 subjects per group is necessary to demonstrate a mean effect of 0.5 at the 5% significance level and a power of 80%. For a larger effect of 0.8, only 26 subjects per group are needed to demonstrate the aforementioned effect. An effect of 0.3, on the other hand, requires a sample size of 175. For an effect of 0.2, a sample size of 252 would be necessary. The above case number estimates were calculated according to the suggestions of Dupont et al. (Dupont et al., 1990). Using nonparametric tests yields similar case numbers. Therefore, when evaluating the studies, even assuming small to medium effect sizes of olfactory therapies, we considered whether or not an effect would have been expected at all given the number of cases examined. This point is particularly important for "small" studies are relevant, which cannot demonstrate an effect of therapy on olfaction. If olfactory dysfunction was not the main target parameter, the studies, and thus possibly the case numbers, are not designed to detect a significant effect in these parameters at all. Ultimately, there remains

then it is unclear whether the non-significance is due to the small number of cases (where an effect actually exists) or to the absence of an effect. If there is a significant effect, it is unclear whether the significant effect is due to chance because the power is probably too low.

The evaluation of the evidence also took into account whether the improvement of olfactory dysfunction was defined as a primary, secondary, or further endpoint, or was not mentioned at all in the study objectives. In other words, this was to test whether the objectives of the study were even designed to demonstrate significant effects of the therapy under investigation on olfaction. Under the aforementioned conditions, RCTs were downgraded to evidence type IIb (RCT with low quality) or intervention studies or case-control studies to evidence type IV. Portions of the literature review are presented in the following sections.

Despite the extensive assessment of the literature, the analysis presented here does not correspond to a systematic review for the overall field of "therapy of olfactory disorders". Due to the inconsistent situation of studies, higher types of evidence could only be identified for individual therapy strategies; for the summary recommendations, a graduation of the recommendation was omitted due to possible gaps in the evidence preparation.

Surgical measures are used with success, especially for sinunasal olfactory disorders, and recommendations from current guidelines and position papers are available for the indication (Damm et al., 2014, Fokkens et al., 2020, Hummel and Welge-Luessen, 2009b, Klimek et al., 1997b, Pade et al., 2008, Strutz et al., 2009, Stuck et al., 2018). Ultimately, the indication for surgical intervention must always be made as a case-by-case decision. Since surgical measures in the area of the nose and paranasal sinuses themselves may be associated with the risk of deterioration of olfactory function (Damm et al., 2002b, Damm et al., 2003, Fokkens et al., 2020, Stuck et al., 2018), no recommendations for the performance of surgical measures have been made in this guideline.

2.6.1 Sinunasal olfactory disorders

2.6.1.1 Acute rhinitis and acute rhinosinusitis

Olfactory disturbances are among the cardinal symptoms of acute rhinosinusitis (Damm et al., 2004, Damm 2009, Fokkens et al., 2020, Stuck et al., 2018). For the diagnosis and treatment of acute rhinitis/rhinosinusitis, evidence-based recommendations are available in the AWMF guideline

"Rhinosinusitis" and in the European position paper on rhinosinusitis and nasal polyps (EPOS) (Fokkens et al., 2020, Stuck et al., 2018). The EPOS provides stratified recommendations (e.g., viral versus bacterial acute rhinosinusitis) on the use of antibiotics, steroids, saline rinses, antihistamines, ipratropium bromide, probiotics, and other therapeutic approaches (Fokkens et al., 2012 and 2020).

Temporary olfactory dysfunction during the acute phase of the disease or of short-term duration afterwards is usually caused by swelling of the mucous membrane in the nose or a decrease in the functional activity of the olfactory epithelium due to inflammation and usually does not require specific diagnosis or therapy (Damm et al., 2014, Damm 2009, Hummel et al., 1998).

However, if the olfactory disorder persists after an otherwise complete clinical healing of the acute rhinitis/rhinosinusitis, i.e., without any other signs of illness, further differential diagnosis is indicated (DD especially postinfectious olfactory disorder) (Damm et al., 2014, Damm et al., 2004, Damm 2007). However, it must be taken into account that the period until the disappearance of all symptoms in acute rhinosinusitis has been defined as "shorter than 12 weeks" (Fokkens et al., 2020). Guidance on the approach to postinfectious olfactory dysfunction can be found in section 1.6.2.1 of this guideline.

Recommendation for therapy of dysosmia in acute (viral/bacterial) rhinitis/rhinosinusitis:

A temporary olfactory disorder in the context of an acute infection of the upper respiratory tract (acute viral or bacterial rhinitis/rhinosinusitis) does not require a separate therapy. Evidence-based recommendations are available for the treatment of acute rhinitis or rhinosinusitis (AWMF guideline "Rhinosinusitis", EPOS). In case of persistence of an olfactory disorder in the

Following an infection with respiratory involvement, postinfectious olfactory dysfunction should be considered as a differential diagnosis.

(Strong consensus)

2.6.1.2 Chronic rhinosinusitis

For the treatment of chronic rhinosinusitis with and without polyposis nasi, evidence-based recommendations are also available in the AWMF guideline "Rhinosinusitis" (Stuck et al., 2018) and in the European position paper EPOS (Fokkens et al., 2020). Pathophysiologically and pathoetiologically, the authors differentiate between chronic rhinosinusitis without and with nasal polyps (polyposis nasi et sinuum), so separate recommendations are given for the two conditions. For chronic rhinosinusitis without nasal polyps in adults, topical steroids and nasal application of saline solutions are recommended; another weak recommendation with a lower level of recommendation is found for long-term therapy with clarithromycin if standard therapy fails. For the treatment of polyposis nasi (CRSsNP and CRScNP: chronic rhinosinusitis cum / sine, chronic rhinosinusitis with nasal polyps) in adults, topical steroids and nasal use of saline solutions are also recommended, in addition to adaptive deactivation for recurrences and ASA hypersensitivity. Further recommendations can also be found in EPOS on surgical therapeutic strategies and on the approach stratified by age (occurrence of the aforementioned conditions in children, adolescents, and adults (Fokkens et al., 2020)). In addition, an update of the chapter on the therapy of chronic rhinosinusitis with polyposis nasi with biologics of the guideline "Rhinosinusitis" is available, which was updated on the principle of a "living guideline" on a S3 level. This guideline contains strong recommendations (recommendation grade A) for the treatment of polyposis nasi with biologics in defined constellations.
(AWMF guideline Rhinosinusitis https://register.awmf.org/de/leitlinien/detail/017-049).
In our own literature review, few placebo-controlled randomized trials were identified and included in a meta-analysis (Hansen et al., 2010, Jankowski et al., 2009, Keith et al., 2000, Lund et al., 2004, Penttila et al., 2000, Small et al., 2005, Small et al., 2008, Stjarne et al., 2006b, Tos et al., 1998, Vlckova et al., 2009), which demonstrated the effect of

topical steroids in patients with sinunasal olfactory disorders (polyposis nasi and chronic rhinosinusitis) on symptom self-assessment. Often, the studies compared different doses of corticosteroid nasal spray versus placebo. When the standardized difference in means was assessed, it was 0.39 for the higher dosage and 0.36 for the lower dosage in favor of the verum arms. According to Cohen, the above values correspond to a weak to moderate treatment effect (Cohen 1988). In none of the aforementioned studies was the therapy effect on olfaction the primary endpoint, so that an evidence type IIb is achieved for topical steroids in sinunasal olfactory disorders based on symptom self-assessments (evidence types of according to Oxford Center for Evidence based Medicine (May 2001, revised 3 2009) for therapy studies).

In addition, other placebo-controlled, randomized, double-blind studies exist that have evaluated the therapeutic effect of topical steroids in polyposis nasi and chronic rhinosinusitis using psychophysical olfactory testing. Some studies (Holmstrom 1999, Lildholdt et al., 1995, Lildholdt et al., 1997, Stjarne et al., 2006a) used (in part) test procedures that did not provide adequate test-retest repeatability. Four studies used the UPSIT (Holmstrom 1999, Keith et al., 2000, Penttila et al., 2000, Stjarne et al., 2006b), and only one study (Penttila et al., 2000) showed a significant effect of cortisone nasal drops on subjective olfactometry. In none of the studies was olfaction the primary endpoint. It is also possible that the mode of application of nasal corticosteroids is an important factor influencing the therapeutic outcome (Damm 2008, Snidvongs et al., 2013, Stenner et al., 2008, Shu et al. 2012).

There are also randomized controlled trials on oral short-term cortisone administration in the literature that investigated the treatment effect on the self-assessment of olfaction of the study participants. Only two of the 4 studies used a placebo control (Hissaria et al., 2006, Van Zele et al., 2010), and both studies reported a significant improvement in the assessment of olfaction in the prednisolone therapy arms. The included number of cases was small, 14 and 20 participants per study arm, respectively, and the treatment effect on olfaction was not the primary endpoint (evidence type IIb). Alobid et al. (Alobid et al., 2006) and Benitez et al. (Benitez et al., 2006) reported on 78 and 84 patient:s with severe polyposis nasi et sinuum, respectively, who had

were assigned to either 14 days of oral prednisolone treatment followed by further treatment with cortisone nasal spray or no therapy (non-placebo-controlled RCT, evidence type IIb). Oral administration of prednisolone resulted in a significant improvement in self-rated olfaction. There may be an overlap between the aforementioned study populations (Alobid et al., 2006, Benitez et al., 2006) (same study site and authors from Barcelona, identical recruitment period, identical oral prednisolone therapy). In addition, other controlled and non-controlled studies exist that also report quite predominantly positive therapeutic effects of oral corticosteroids (Blomqvist et al., 2001, Blomqvist et al., 2009, Damm et al., 1999, Hessler et al., 2007, Jankowski et al., 2003, Martinez-Devesa et al., 2011, Tuncer et al., 2003). Analogous to topical corticosteroids, only very sporadic results from controlled intervention studies are available (Heilmann et al., 2004) that have evaluated the therapeutic success of systemic corticosteroids using validated psychophysical testing methods. In addition to the evidence-based assessment in EPOS (Fokkens et al., 2020), a Cochrane Library review (Martinez-Devesa et al., 2011) is also available on the general treatment effects of oral corticosteroids for nasal polyps.

Furthermore, there are indications for (adjuvant) therapeutic effects on olfaction by other agents/treatment strategies, some of which are applied in addition to oral and topical corticosteroids.

The effects of aspirin deactivation on dysosmia have been investigated in a placebo-controlled ranomized controlled trial (RCT, Stevenson et al., 1984), two prospective intervention studies (Lee et al., 2007, Rozsasi et al., 2008), two case-control studies (Havel et al., 2013, Sweet et al., 1990) and several uncontrolled studies (Berges- Gimeno et al., 2003a, Berges-Gimeno et al., 2003b, Comert et al., 2013, Gosepath et al., 2001, Gosepath et al., 2002, Kutlu et al., 2013, Merkonidis et al., 2012, Stevenson et al., 1996). The included subjects suffered from aspirin-exacerbated respiratory disease (AERD). While the placebo-controlled RCT by Stevenson et al. (Stevenson et al., 1984) did not demonstrate significant effects on olfaction, all other studies (evidence types IIb to IV) reported positive effects on olfaction. Symptom self-assessments were used in almost all studies. Due to methodological problems and inadequate study quality (e.g., insufficient

disease definitions, presentation of the additional drugs used or the results on olfaction), a conclusive effect assessment on olfaction does not seem possible today.

Several RCTs and a meta-analysis (Wentzel et al., 2013) are available on the efficacy of leukotriene receptor antagonists in chronic rhinosinusitis with nasal polyps, which have investigated the efficacy of montelukast and zafirlukast, respectively. Pauli et al. (Pauli et al., 2007) and Schäper et al. (Schäper et al., 2011) evaluated the efficacy of 10 mg montelukast for 4 and 6 weeks, respectively, without additional intranasal or systemic corticosteroid medication in placebo-controlled RCTs. Montelukast showed significant improvement in symptom scores, the overall sample size was small with 30 (Pauli et al., 2007) and 24 (Schäper et al., 2011) subjects, respectively, and olfactory dysfunction was not the primary endpoint of the studies (evidence type IIb). Two RCT compared the efficacy of montelukast versus topical steroids following sinus surgery in patients with chronic rhinosinusitis and nasal polyps (Mostafa et al., 2005, Vuralkan et al., 2012) (evidence type IIb). In the study by Vuralkan et al, treatment (n = 50) with montelukast was shown to be superior to that with topical steroids of self-assessment of olfaction. In contrast, Mostafa et al. (n = 40) reported superiority of topical steroids. Another controlled trial randomized 38 participants, all of whom had already received oral prednisolone therapy for 14 days and intranasal corticosteroids for 8 weeks, to either unchanged topical continuation therapy or topical continuation therapy and the addition of montelukast for 8 weeks (Stewart et al., 2008). The two treatment arms did not differ with respect to self-assessment of olfaction (evidence type IIb). In addition, there are other low-level evidence case series on the 5-lipoxygenase inhibitor zileuton (Dahlen et al., 1998, Kieff et al., 2005, Parnes et al., 2000, Ragab et al., 2001, Wentzel et al., 2013). Leukotriene antagonists therefore appear to be an interesting treatment strategy to improve olfaction in chronic rhinosinusitis with nasal polyps. Larger placebo-controlled RCTs with validated psychophysical testing procedures are needed to clarify efficacy with certainty.

Two randomized, double-blind, placebo-controlled trials have examined the effects of roxithromycin (Wallwork et al., 2006) and azithromycin (Videler et al., 2011) in chronic rhinosinusitis. The study by Wallwork et al. 2006 examined the

effect on olfaction using the Sniffin' Sticks test, Videler et. al. 2011 used analog scales. No significant effect was observed during the 12-week study period.

For other therapeutic approaches in chronic rhinosinusitis with and without nasal polyps, further studies are needed to assess the therapeutic effects in an evidence-based manner (e.g., furosemide (Kroflic et al., 2006), nasal lavage (Bachmann et al., 2000, Chong et al., 2016, Hartog et al., 1997, Jiang et al., 2008, van den Berg et al., 2014)). In the case of unsuccessful conservative therapy, surgical measures for the treatment of chronic rhinosinusitis without and with nasal polyps can also be considered, which aim to improve the underlying disease and whose indication must be made as a case-by-case decision, taking into account the recommendations of the standard literature and the topic-related guidelines (Croy et al., 2010, Damm et al, 2014, Damm et al, 2002a, Fokkens et al, 2020, Hummel and Welge-Luessen, 2009b, Klimek et al, 1997b, Pade et al, 2008, Schriever et al, 2013, Strutz et al, 2009, Stuck et al, 2012, Welge-Lüssen et al, 2009). In case of a surgical approach, it should be noted that nasal surgery may also be associated with a risk of deterioration of olfactory function (Damm et al., 2003, Fokkens et al., 2020, Hummel and Welge-Luessen, 2009b, Pade et al., 2008, Strutz et al., 2009, Stuck et al., 2018).

Monoclonal antibodies (biologics) are a class of drugs that are increasingly used to treat chronic rhinosinusitis with polyposis nasi and thus also for corresponding inflammation-related olfactory disorders (AWMF guideline Rhinosinusitis (Pfaar et al. 2023), Fokkens et al. 2020).

Dupilumab is a human monoclonal antibody against the alpha subunit of interleukin (IL)-4 that inhibits IL-4 and IL-13 signaling and is approved for use in CRSwNP (chronic rhinosinusitis with nasal polyps, polyposis nasi et sinuum). Previously in a 2016 study, Bachert et al. demonstrated that odor identification (as measured by the UPSIT) improved significantly after 16 weeks of dupilumab (600mg starting dose and 300mg weekly) in a multicenter placebo-controlled study of 60 patient:s (Bachert et al., 2016). Bachert and colleagues reported results from additional studies in this indication in 2019 (LIBERTY NP SINUS-24 and LIBERTY-NP SINUS-52, two multicenter, randomized, double-blind, placebo-controlled

Parallel group phase 3 studies with dupilumab 300 mg every two weeks in patients with severe CRSwNP) (Bachert et al. 2019). Using odor identification tests (UPSIT) and self-assessments, the significantly improved olfaction compared to controls was demonstrated at 24 and 52 weeks. These olfactory outcomes were examined in more detail by Mullol and colleagues in 2022, who performed a pooled analysis of the 724 patient:ins in the two studies (Mullol et al. 2022). They showed rapid (subjective improvement in scores by day 3) and sustained improvement in olfactory function (mean UPSIT- score improvement of 10.5 at 24 weeks) in the dupilumab group compared with the control group. These results were independent of various potential confounding factors, such as disease duration, previous surgery, and additional respiratory disease.

Omalizumab is a recombinant humanized monoclonal antibody that binds to freely circulating IgE, thereby decreasing the expression of IgE receptors on mast cells, dendritic cells, and basophil cells, thereby inhibiting their activation. In 2010, Pinto and colleagues conducted a double-blind, placebo-controlled, randomized trial in 14 patient:s with treatment-refractory CRS (treatment n=7, control n=7) (Pinto et al. 2010). After 6 months of treatment with omalizumab, there was no significant improvement in UPSIT outcomes compared to controls. In 2013, Gevaert et al. also conducted a placebo-controlled randomized trial (24 patient:s with CRSwNP, treatment n=16, control n=8) (Gevaert et al. 2013). They showed significantly improved subjective symptom scores for "loss of smell" in the treatment group, but did not examine olfactory function with psychophysical instruments. However, a more recent paper by Gevaert et al. from 2020 (POLYP 1 and 2) with a larger collective showed an improvement in UPSIT after 24 weeks of therapy with omalizumab with a statistically significant difference compared to placebo (mean difference between both groups compared to baseline UPSIT 3.86) (Gevaert et al. 2020).

Mepolizumab is an anti-IL5 monoclonal antibody that interferes with the differentiation and survival of eosinophil granulocytes. In a double-blind, placebo-controlled, randomized trial, Bachert and colleagues demonstrated significantly improved subjective

odor values) (Bachert et al. 2017). However, there was no significant improvement in odor identification scores (12-item screening test - sniffin sticks). In a double-blind, placebo-controlled, randomized trial of 30 patient:s with corticosteroid-refractory CRSwNP, Gevaert et al. demonstrated a long-lasting improvement in subjective olfactory function after treatment with mepolizumab. However, this improvement did not reach statistical significance compared to controls, and no psychophysical tests were performed (see Mullol et al. 2022).

Despite the still limited data available, it can be summarized that in the studies with a representative sample size and validated psychophysical olfactometry, clear therapeutic effects on olfaction with biologics can be identified (especially for dupilumab). The therapeutic effects on olfaction may partly lag behind the effects on other symptoms (e.g., regression of nasal polyps, nasal obstruction), since irreversible damage/changes to the olfactory epithelium may already be present in addition to functional limitations, especially in long-term courses.

Recommendation for therapy of dysosmia in chronic rhinosinusitis with/without nasal polyps.

Sinunasal dysosmia in the setting of chronic rhinosinusitis with or without nasal polyps should be treated with an evidence-based, guideline-driven therapeutic trial to improve the underlying condition.

For this purpose, stratified and evidence-based recommendations (partly at the highest level of evidence) are available from the updated German guideline and the European position paper on rhinosinusitis and polyposis nasi (EPOS). The treatment recommendations mentioned there may have a smaller therapeutic effect on the symptom "olfactory dysfunction" than on the overall disease.

If treatment of the underlying disease with biologics is being considered, dupilumab (or possibly omalizumab, but possibly smaller effects) should be used first if the treatment of the olfactory disorders is the primary concern.

(Strong consensus)

2.6.1.3 **Allergic rhinitis:**

The German Society of Allergology and Clinical Immunology (DGAI) published a guideline on allergic rhinoconjunctivitis in 2003 (Bachert et al., 2003). Within the framework of the ARIA initiative, an expert group of the World Health Organization (WHO) has developed evidence-based recommendations for the diagnosis and therapy of allergic rhinitis; the current version dates from 2012 (Bousquet et al., 2012). The therapy recommendations of the ARIA working group on allergic rhinitis and related or associated diseases are based on a comprehensive systematic analysis of the available literature. A new guideline on allergen immunotherapy for allergic rhinitis exists from 2014 (Pfaar et al., 2014). The aforementioned guidelines and position papers can be used to select an appropriate therapeutic approach to improve the underlying disease. However, olfactory dysfunction is not one of the main symptoms of allergic rhinitis. A systematic literature review on dysosmia in allergic rhinitis was published by Stuck and Hummel in 2015 (Stuck and Hummel, 2015). Data on the frequency of olfactory dysosmia in allergic rhinitis vary in the literature from 10% to 88%, with most studies reporting rates of 20% to 40% (Stuck and Hummel, 2015). Stuck and Hummel further concluded that allergic rhinitis does not usually lead to severe olfactory impairment in affected patient:s, but olfactory dysfunction may increase with disease severity. In other words, olfactory dysfunction is likely to be more severe in patients with persistent/perennial allergic rhinitis than in intermittent/seasonal allergic rhinitis. A multicenter study demonstrated that in a cohort of over 1200 children with untreated allergic rhinitis aged 6-12 years, 44% of children reported olfactory dysfunction (Langdon et al., 2016). Among these, the frequency was significantly higher in children with persistent rhinitis than in children with intermittent allergic rhinitis. The more severe the rhinitis symptoms were in the children and the longer the disease persisted, the more pronounced the olfactory loss was.

In allergic rhinitis, the treatment effect of topical and systemic antihistamines, topical corticosteroids, and allergen immunotherapy on symptom self-assessment and psychophysical testing, respectively, has been investigated in studies (Damm 2008, Stuck et al., 2015).

The effects of topical and systemic antihistamines were investigated in 3 randomized controlled trials (one placebo-controlled trial) and one uncontrolled trial. Guilemany et al. reported an improvement in self-assessment in the verum group with levocetirizine, but not in the so-called Barcelona Smell Test-24 (Guilemany et al., 2012). Gambardella could not find any difference in efficacy between loratadine tablets and azelastine nasal spray (Gambardella R. 1993). The aforementioned studies had total sample sizes of 27 and 30 study participants, respectively (Gambardella R. 1993, Guilemany et al., 2012), so smaller treatment effects may not have been detected. Kalpaklioglu and Kavut compared a cortisone nasal spray with azelastine nasal spray in subjects with allergic and non-allergic rhinitis, positive treatment effects could not be detected (Kalpaklioglu et al., 2010). Only the uncontrolled study by Wober et al. reported positive therapy effects (Wober et al., 1997).

Topical corticosteroids have been used in 5 studies (4 RTC, 1 uncontrolled study) in patient:s with allergic rhinitis (Stuck et al., 2015), and treatment effects were assessed with either symptom self-assessments and/or psychophysical testing. Two of the 4 RTC and the uncontrolled study had a total sample size of 25 participants or less each (Golding-Wood et al., 1996, Higaki et al., 2012, Sivam et al., 2010, Stuck et al., 2003). Positive treatment effects were observed by Sivam et al. (self-assessment, not UPSIT) and by Stuck et al. (olfactory threshold in the Sniffin' Sticks test) (Sivam et al., 2010, Stuck et al., 2003). The placebo-controlled RCT by Higaki et al. had 25 participants per study arm, and self-assessment of olfactory function remained without significant differences between the 3 groups, regardless of therapy with mometasone nasal spray (Higaki et al., 2012). The study by Kalpaklioglu and Kavut has already been mentioned in antihistamines (allergic rhinitis, n=69), triamcinolone nasal spray had no positive treatment effect on symptom self-assessment on olfactory function (Kalpaklioglu et al., 2010). The sample size was adequate with 120 participants in the placebo-controlled RCT study by Meltzer et al. The treatment effect on olfaction was assessed with the CCCRC test (compare section 1.5.1 (2)) (Meltzer et al., 1998). The mometasone nasal spray significantly improved monorhinal tested odor identification in the verum group. The butanol-swelling test of the CCCRC, which showed insufficient repeatability

was also performed, but (as expected) without significant improvement.

In a multicenter observational study by Klimek et al., a nasal spray with the active ingredient combination of a corticosteroid (fluticasone propionate) and an antihistamine (azelastine) showed a significant improvement in olfaction in 47 patients with persistent allergic rhinitis. (Klimek et al., 2017) Olfactory ability was assessed with the SDI at baseline and after 1 and 3 months. In addition to the olfactory ability, the subjective self-assessment of nasal symptoms also improved.

The efficacy of the leukotriene antagonist montelukast compared to mometasone furoate in patients with allergic rhinitis was investigated in a study by Dalgic et al. (Dalgic et al., 2017) In a prospective, randomized, parallel-group study with three arms (montelukast vs. mometasone furoate vs. montelukast and mometasone furoate), the authors found a significant improvement in olfactory performance measured by Sniffin` Sticks only in the groups of patients receiving mometasone furoate. It should be noted that only 10 to 11 patients per study arm were included.

For allergen immunotherapy, there are 5 studies that have determined therapy effects on olfaction. 4 of the 5 studies were uncontrolled case series and therapy effects were determined using the Sniffin' Sticks test and/or symptom self-assessments (Chang et al., 2009, Damm 2008, Radcliffe et al., 1996, Stuck et al., 2015). The randomized, double-blind, placebo-controlled study by Radcliffe et al. used a total sample size of 36 subjects and used what is known as "low dose immunotherapy" (Radcliffe et al., 1996). All studies reported an improvement in olfaction. Taking into account the criteria mentioned in section 1.6, the number of cases included by Radcliffe et al. in particular appears unsuitable for assuming a reliable therapeutic effect, so that a maximum of evidence type 4 can be derived from the data available to date.

A study by Shin and co-workers investigated the relationship between vitamin D serum levels and olfaction in children. (Shin et al., 2021) For this purpose, 512 children aged 10-12 years were tested using the threshold test of the Sniffin' Sticks test battery.

was investigated. It was found that children with reduced olfactory ability also had reduced vitamin D serum levels. It should be noted that the study was conducted as a cross-sectional study without a control group. Furthermore, the study could neither answer the question whether an improvement of the olfactory ability could be expected with a substitution of vitamin D, nor how the observed correlation could be explained.

In summary, the results of most studies do not allow a reliable assessment of possible therapeutic effects on olfaction or a differentiation from spontaneous remission due to methodological weaknesses (especially inadequate sample size; study design). This is especially true for antihistamines and allergen immunotherapy. Only the RCT on mometasone by Meltzer et al. is an exception, with only the identification test of the CCCRC, but not the olfactory threshold test, showing sufficient repeatability (evidence type IIb) (Meltzer et al., 1998).

Recommendation for the therapy of dysosmia in allergic rhinitis

For the underlying disease "allergic rhinitis", various consensus- and evidence-based therapy recommendations are available (e.g. ARIA, guidelines of the AWMF and DGAKI), whose influence on olfaction cannot be conclusively assessed at present due to the unsatisfactory literature situation. If an attempt to treat dysosmia in the context of allergic rhinitis is made, topical steroids may be the most promising therapeutic option.

(Strong consensus)

2.6.1.4 Other forms of rhinitis

Non-allergic rhinitis is an umbrella term for various forms of rhinitis, the most common form being so-called idiopathic rhinitis (reviews in (Bernstein 2013b, Bernstein 2013c, Settipane et al., 2001, Settipane 2011, Settipane et al., 2013)). There are few studies in the literature on olfactory impairment in nonallergic rhinitis, and the exact frequency and extent of olfactory impairment is unknown, as is the exact pathophysiology (Baraniuk et al., 2009, Bernstein 2013b, Bernstein 2013c, Bousquet et al., 2008, Damm 2006, Damm 2009, Hummel et al., 2007, Settipane et al., 2001, Settipane 2011, Settipane et al., 2013). The perception of odors can trigger rhinitis symptoms in affected individuals (gustatory rhinitis (Bernstein et al., 2011b, Bernstein 2013a, Settipane et al., 2013)). Only a subset of studies have investigated the effects of medication on olfaction in patients with non-allergic rhinitis (Bernstein 2013c, Long et al., 2002, Settipane 2011, Settipane et al., 2013).

In 2002, the New England Medical Center Evidence-based Practice Center and the Agency for Healthcare Research and Quality examined the efficacy of drug therapy for non-allergic rhinitis in a systematic literature review covering the years 1966-2000 (Long et al., 2002). There, the treatment effects of 12 RCT were evaluated (a review can be found in (Damm 2006) together of two placebo-controlled studies on azelastine (Settipane et al., 2001), on fluticasone (three studies) and on capsaicin (one study) (van Rijswijk et al., 2003)).

The anticholinergic ipratropium bromide works well against rhinorrhea in nonallergic rhinitis, with a daily dose of 80-100mg appearing sufficient (Long et al., 2002).

The main field of application are patients of the "runner" type (Bronsky et al., 1995, Long et al., 2002). To the best of our knowledge, the influence on olfaction has been investigated in uncontrolled studies.

The topically applied antihistamine azelastine can also achieve a significant improvement of the main symptoms (rhinorrhea, sneezing, obstruction, mucous throat ["postnasal drip"]) in non-allergic rhinitis (Banov et al., 2001, Bernstein 2007, Bernstein et al., 2009, Ciprandi 2004, Long et al., 2002, Settipane 2011). However, also noteworthy in the aforementioned studies is the "placebo effect" (saline nasal spray), where 73% of IR patient:s responded to treatment (Settipane 2011). Olfaction was not assessed in the majority of available RCTs; Gehanno et al. did not find an effect on olfaction in their placebo-controlled RCT (n = 89) in patients with non-allergic rhinitis (Gehanno et al., 2001). This contrasts with the study by Klimek et al. (2017), who demonstrated a significant effect on olfaction as measured by self-assessments and Sniffin' Sticks olfaction tests in 47 patients with perennial allergic rhinitis after therapy with azelastine (1 spray per side, 2 times daily, for 3 months). Topical corticosteroids also achieved significant efficacy over placebo medication on all major symptoms of idiopathic rhinitis (obstruction, rhinorrhea, post nasal drip) in several RCTs (Long et al., 2002, Webb et al., 2002). A dose of 400/800 µg/d budesonide or 200/400 µg/d fluticasone seems adequate. Efficacy may be stronger in inflammatory forms of nonallergic rhinitis (Kirtsreesakul et al., 2015). However, the study situation also justifies a therapy trial with topical corticosteroids also in patient:s with non-inflammatory, non-allergic rhinitis (Bernstein 2013c, Long et al., 2002, Settipane et al., 2001, Settipane 2011). The effect on olfaction is less well documented. Kirtsreesakul et al. (Kirtsreesakul et al., 2015) examined the effects of triamcinolone at a daily dose of 220 µg on symptom self-assessment applied over 4 weeks by subjects with allergic rhinitis (n = 82) and nonallergic rhinitis (n = 67). Olfactory ability improved significantly with therapy, with no differences between the two groups.

Several placebo-controlled RCTs are available on the efficacy of capsaicin (8-methyl-N-vanillyl-6-nonenamide) in nonallergic rhinitis, as well as a systematic

Literature review available (Bernstein et al., 2011a, Blom et al., 1997, Gevorgyan et al., 2015, van Rijswijk et al., 2003). Degeneration of C-fibers and downregulation of transient receptor potential vanilloid (TRPV) receptor expression in sensory C-nerve fibers are discussed as mechanisms of action (Bernstein et al., 2015, van Rijswijk et al., 2006). TRPV is a specific ion channel involved, for example, in the perception of pain, temperature, and pressure. The therapeutic capacities of capsaicin differ significantly in different forms of rhinitis (e.g., insufficient efficacy in allergic rhinitis (Cheng et al., 2006)). While there was a significant reduction in rhinitis symptoms in terms of a long-term effect in the verum groups, among others, capsaicin had no effect on the concentration of leukotrienes, prostaglandins, or tryptase in nasal secretions (Blom et al., 1997, Gevorgyan et al., 2015; Van Gerwen et al. 2021). However, the treatment does not seem to have an effect on olfaction, which was tested in the study by van Rijswijk et al. using the UPSIT test (van Rijswijk et al., 2003).

Toxic-irritant rhinitis can be triggered by a variety of gases and aerosols, but exact epidemiological data on the frequency or extent of olfactory disturbances, therapeutic options other than abstinence measures are not known. (Reviews in (Drake-Lee et al., 2002, Groneberg et al., 2003, Hummel and Welge- Luessen, 2009b, Muttray et al., 2006, Settipane 2011, Shusterman 2007, Slavin 2003, Zhao et al., 2004).

In summary, for nonallergic forms of rhinitis, there is no evidence of efficacy from placebo-controlled RCTs with adequate numbers of cases that have examined treatment effects with reproducible psychophysical testing procedures on olfaction.

Recommendation for the treatment of dysosmia in non-allergic/idiopathic rhinitis.

For non-allergic/idiopathic rhinitis, based on the current literature and the largely unexplained pathophysiology, the only recommendation regarding olfactory disorders is to attempt individual therapy to improve the underlying disease. This applies analogously to other forms of rhinitis with unexplained pathophysiology. In the case of olfactory disturbances in toxic-irritant rhinitis, the focus is on abstinence measures.

(Strong consensus)

2.6.2 Non-sinunasal dysosmia

For non-sinunasal olfactory disorders, very different therapeutic strategies are used in practice and in the literature (Damm et al., 2004, Hummel and Welge- Luessen, 2009b). If the olfactory disorder can be traced back to a triggering underlying disease, the treatment of the underlying disease is in the foreground (Forster et al., 2004, Hummel and Welge-Luessen, 2009b).

2.6.2.1 Postinfectious dysosmia

About one third of patients with prolonged postinfectious dysosmia experience spontaneous improvement within 12 months (Hummel 2000, Hummel and Welge-Luessen, 2009b). In some cases, even higher spontaneous remission rates are reported (Duncan et al., 1995a). In the delta variant of SARS-CoV 2 associated olfactory disorders, there is typically a complete loss of smell during the acute infection, which then improves after a short period of time in a large proportion of patients. Approximately 6 months after a corona-related infection, more than 80% of affected individuals report extensive recovery (Isenmann et al., 2021). In patients with a longer lasting olfactory disorder, partial recovery only occurs over the course of months and years (Trecca et al. 2022; Tan et al. 2022).

The ability of olfactory receptor cells to regenerate is thought to correlate negatively with age and duration of disease. That is, younger patients may have a greater chance of spontaneous improvement (Hummel and Welge-Luessen, 2009b; Isenmann et al., 2021). The longer the disorder has lasted and the more olfactory cells have been damaged (Conley et al., 2003), the more difficult spontaneous regeneration becomes (Hummel and Welge-Luessen, 2009b, Reden et al., 2006b; Tan et al. 2022).

A wide variety of drug therapy approaches have been investigated for postinfectious olfactory disorders (reviews in Patel et al. 2022, Hura et al. 2020; Hummel et al. 2017). Some of these studies will be outlined below.

Topical and oral steroids were used by Heilmann et al. and Stenner et al. (Heilmann et al., 2004, Stenner et al., 2008). Heilmann et al. reviewed the efficacy of topical and systemic corticosteroids and vitamin B complex on olfactory dysfunction with sinunasal n=19), postinfectious (n=72), posttraumatic (n=10), idiopathic n=85), and other (n=6) causes (total n= 192 (Heilmann et al., 2004)) in a complex, open intervention study. The effect on olfaction was the primary endpoint of the study (evidence type IIb). Unfortunately, the presentation of the results of the Sniffin' Sticks tests was not done in dependence of the cause of the olfactory disorder, so that no exact conclusions could be drawn between the described significant treatment effects and postinfectious dysosmia (or even in olfactory disorders of other etiology). This applies in an analogous way to the therapeutic approach with vitamin B complex.

In a retrospective study, Stenner et al. (2008) investigated the efficacy of systemic and topical corticosteroids in olfactory dysfunction of various causes (total n = 89, evidence type III). Subjects with postinfectious dysosmia (n = 30) improved 50% on administration of low-dose oral betamethasone for 20 days in the Sniffin' Sticks test. Additional positive treatment effects were described for topical therapy with budesonide or budesonide neomycin for 12 weeks. The therapy effects reported by Stenner et al. are above the expected spontaneous remission of postinfectious olfactory disorders (Damm et al., 2013, Stenner et al., 2008). In a retrospective study by Hintschich et al. (2022), however, no effect of treatment with mometasone nasal spray together with olfactory training (n=40) compared to olfactory training alone (n=46) was shown in patients with COVID-associated olfactory loss.

Ginkgo Biloba was applied by Seo et al. (Seo et al., 2009) in combination with topical and systemic steroids (RCT without placebo control, study arm 1: prednisolone 30mg descending over 14 days, mometasone over 4 weeks (n = 28), study arm 2: medication on study arm 1 plus Ginkgo Biloba (n = 43), evidence type IIb). The additional application of Ginkgo Biloba did not yield an additional significant effect, although an improvement in olfactory performance in the BTT/CCCRC identification test was observed by therapy in 32% (corticosteroids only) and 37% (corticosteroids plus Ginkgo Biloba), respectively (the threshold test BTT of the CCCRC has insufficient reproducibility).

Quint et al. (Quint et al., 2002) evaluated the efficacy of Caroverin (120 mg/d) and zinc (400 mg/d) over 4 weeks in a total of 77 subjects with postinfectious (n = 38), posttraumatic, and idiopathic olfactory disorders using the Sniffin' Sticks test (RCT without placebo control, evidence type IIb). Results were presented stratified into the categories of anosmia and hyposmia. Quint et al. observed a significant improvement in the olfactory threshold of the anosmic subjects with postinfectious and posttraumatic olfactory disorders, as well as in identification performance, regardless of the quantitative extent of the olfactory disorder. However, the exact improvement in the postinfectious olfactory disorder group cannot be determined from the publication. Zinc, on the other hand, showed no efficacy.

Zinc has been used in other studies. Henkin et al. (Henkin et al., 1976) investigated the efficacy of zinc sulfate (100mg/d) over 12 and 24 weeks in a single-blind placebo-controlled RCT with 106 study participants, including 45 subjects with post-infectious olfactory dysfunction (evidence type IIb). Treatment outcome was evaluated by determining perceptual and recognition thresholds for pyridine, nitrobenzene, and thiophene; data on repeatability of these procedures are not available. Treatment with zinc produced no advantage over placebo.

Aiba et al. (Aiba et al., 1998) reported in a retrospective case series on 426 patients with dysosmias of various causes (postinfectious n = 184, posttraumatic n = 95, unknown = 147) who were treated either with zinc sulfate (300 mg/d, n = 25), standard therapy with vitamin B complex and topical corticosteroids (n = 159, no details on dosage), or with a combination of zinc sulfate and standard therapy for more than one month (evidence type IV). The success of therapy was graded on a 7-step ranking scale between "complete recovery" and "worsening" was assessed. For post-infectious and "unknown" olfactory disorders, the treatment did not yield any significant difference between the therapy groups, only for post-traumatic olfactory disorders there was a difference in favor of zinc therapy alone or combined. Due to the methodology used by Aiba et al. the significance of the above results remains unclear.

Duncan et al. compared different forms of vitamin A administration (intramuscular injection (n = 52), tablets (n = 3), oral emulsion (n = 1)) in a total of 56 subjects with postinfectious (n = 21), idiopathic (n = 18), and dysosmia of other cause

(post-traumatic, toxic, postoperative, etc.) over 6 to 12 weeks in different doses (evidence type IV). Therapy effects were assessed by self-assessment and a non-validated test procedure ("standard forced choice three stimulus sniff technique"), and the presentation of results was also inadequate and difficult to interpret. A "marked improvement to complete recovery" was reported in 38 of the 56 subjects; in the postinfectious olfactory disorders group, 16 of 21 subjects improved.

Reden et al. (Reden et al., 2012) reviewed the efficacy of vitamin A at a dosage of 10,000 units per day for 3 months for postinfectious and posttraumatic dysosmia using the Sniffin' Sticks test in a placebo-controlled RCT with 52 participants. Although Sniffin' Sticks test scores improved significantly in the overall group, verum therapy was not shown to be superior to the placebo arm. Critically, the sample size was insufficient to detect small to moderate treatment effects (no evidence of effect, evidence type IIb).

A retrospective study (Hummel et al. 2017) on a total of 171 patients on the efficacy of topical vitamin A (10,000 i.U. over 8 weeks) together with olfactory training (see below) in patients with postviral and postinfectious olfactory disorders showed a significant improvement (comparison between olfactory training and olfactory training plus vitamin A application: Improvement in 23% and 37%, respectively).

Hummel et al. (Hummel et al., 2002) also tested the efficacy of 4 months of alpha-lipoic acid (600 mg/d) in 23 subjects with postinfectious dysosmia in an uncontrolled study using the Sniffin' Sticks test (evidence type IV, small sample size). An increase in SDI score of at least 5.5 points was observed in 61% of study participants, appearing higher than the spontaneous remission rate expected from the literature (Damm et al., 2013). However, the assumption of alpha-lipoic acid efficacy needs to be substantiated in further studies with larger numbers of participants and a control group.

Reden et al. (Reden et al., 2011) investigated the efficacy of oral minocycline (100 mg/d) using the Sniffin' Sticks test in 55 subjects with postinfectious dysosmia (placebo-controlled RCT). It must be critically noted that the number of subjects in the treatment arms was too small to reliably detect small to moderate effects.

(no evidence of efficacy, evidence type IIb). An efficacy compared to the placebo control could not be observed.

Henkin et al. published 2 studies on the efficacy of theophylline for olfactory disorders of various causes (Henkin et al., 2009, Henkin et al., 2012b).

In an open-label controlled intervention study (Henkin et al., 2009), a total of 312 patients (postinfectious: n = 97, allergic rhinitis n = 97, posttraumatic n = 42, other causes n = 76) were treated with an initial dose of 200 mg/d theophylline (evidence type III). In the absence of treatment success, the therapeutic dose was increased to 400, 600, or 800 mg/d, and treatment lasted up to 72 months. Henkin et al. reported treatment success in a total of 50.3% of study participants taking theophylline, and 10.9% would have normalized olfactory function. Treatment success would be tied to sustained use of theophylline and showed dose dependence. Treatment outcome was evaluated by determining perceptual and recognition thresholds for pyridine, nitrobenzene, thiophene, and amyl acetate; data on sufficient test-retest repeatability are not available for this procedure (evidence type IV, devaluation due to questionable repeatability of the psychophysical testing used).

In a pilot study, Henkin et al. (2012b) investigated the efficacy of nasal application of theophylline compared with oral application in 10 subjects with hyposmia (cause: post-infectious, post-traumatic, allergic rhinitis, evidence type IV). Nasal application of theophylline for 4 weeks improved olfaction in 8 of 10 subjects. For the evaluation of the therapy effects, a determination of the perception and recognition thresholds for pyridine, nitrobenzene, thiophene and amyl acetate was used again (evidence type IV).

In a prospective intervention study, Vent et al. (Vent et al., 2010b) compared the efficacy of acupuncture and traditional Chinese medicine (TCM) with vitamin B complex administration in a total of 30 subjects with postinfectious olfactory dysfunction. The combination of acupuncture plus TCM was significantly more effective in the Sniffin' Sticks test (evidence type III; see also Drews et al. 2021). Further studies on acupuncture are only available in normosmic subjects (Anzinger et al., 2009, Tanaka et al., 1999).

Several studies are available on the potential efficacy of topical sodium citrate, which overall suggest a weak effect of sodium citrate (Panagiotopoulos et al. 2005; Whitcroft et al. 2016, 2017, 2021; Philpott et al. 2017). These effects may be much stronger for other chelating substances such as nitrilo-triacetate sodium or pyrophosphate sodium (Abdelazim et al. 2022a; Abdelazim et al. 2022b).

Olfactory training has been investigated by several studies in postinfectious dysosmia (Hummel et al., 2009a; Sorokowska et al. 2017). The results of a prospective intervention study by Hummel et al. (Hummel et al., 2009a) showed in 24 subjects with postinfectious olfactory dysosmia that structured olfactory training over 12 weeks can lead to an improvement in olfaction (improvement in 5/24 with training, in 0/11 without training, evidence type III). The subjects trained twice daily with 4 scents: rose, eucalyptus, lemon, and clove. Hummel et al. suggested that olfactory training may lead to improved regeneration of olfactory receptor neurons (Livermore et al., 1996, Wang et al., 2004; Kim et al. 2019).

Damm et al. conducted a randomized, pseudo placebo-controlled (2 training groups: 1st group trained with high concentration of fragrance (undiluted); 2nd group trained with low concentration of fragrance (10th percentile of perceptual threshold), single-blinded cross-over study with 171 subjects with postinfectious olfactory dysfunction (Damm et al., 2013). Participants were randomized into two groups receiving olfactory training with suprathreshold and near-threshold odorant concentrations, respectively. After 18 weeks, a cross-over took place; in total, the subjects trained for 36 weeks. The odorants were presented with the aid of so-called olfactory training pens (rose, eucalyptus, lemon and clove, following the methodology of Hummel et al. 2009). Assuming carry-over effects, only the first training period was significantly evaluated. After 18 weeks, a significant improvement in olfactory function (defined as an increase in the SDI score in the Sniffin' Sticks test of six or more points) was observed in 26% of those training with a high fragrance concentration compared to 15% in the group with a low fragrance concentration. When considering patients with post-infectious olfactory dysfunction for less than one year, the results were even more pronounced. 63% of the patients benefited from a training with

high-concentration fragrances, whereas olfaction improved in only 19% of the low-concentration comparison group (evidence type Ib).

An uncontrolled study of 39 subjects with postinfectious olfactory dysfunction by Geissler et al. also reported a significant improvement in Sniffin' Sticks Test (SDI) scores after a training period of 32 weeks (Geissler et al., 2014). However, in this study, the subject:ing number was borderline small and a control group was lacking, which is problematic given the expected small to moderate therapeutic effects of olfactory training and the relatively high spontaneous recovery rate in postinfectious olfactory disorders (Evidence Type IV).

Altundag et al. studied subjects with postinfectious dysosmia in a prospective intervention study who were assigned to 2 therapy arms or one arm without structured olfactory training (evidence type IIb (Altundag et al., 2015)). In the first therapy arm, subjects trained with 4 scents using the method proposed by Hummel et al. in 2009, and in the second with 12 different scents over 36 weeks. The study included a total study population of 85 participants, so the group size was borderline large in terms of the expected therapy effects. While there was no improvement in SDI score after 36 weeks without scent training (18.0 versus 19.7 points), training without scent switching showed an average SDI increase from 18.2 to 24.3 points and scent training with a total of 12 scents from 18.1 to 26.3 points. The authors concluded that increasing the duration of training and changing the odors used improved the efficacy of the treatment and that success was also dependent on starting the olfactory training in a timely manner.

A review of the efficacy of olfactory training for olfactory disorders can be found in Sorokowska et al. (2017), Helman et al. (2022), and also Patel et al. (2021) - its use for postviral and, with limitations, post-traumatic olfactory disorders is recommended in these reviews.

Regarding therapy for SARS-CoV 2 associated olfactory disorders, there have been a number of publications since 2020, including theophylline (Gupta et al. 2022), palmitoylethanolamide and luteolin (d'Ascanio et al. 2021), platelet-rich plasma (Yan et al. 2020; Steffens et al. 2022), or omega 3 (Yan et al. 2020; Hernandez et al. 2022), referring to the relevant reviews (e.g., Hura et al. 2020; Patel et al. 2022). It is expected,

that the value of these therapeutic options will become clear in the course of follow-up studies over the next few years.

In summary, a positive therapeutic effect of structured olfactory training in postinfectious olfactory dysfunction can be deduced from the results of the scientific literature. Whether structured olfactory training is also effective in dysosmias of other causes needs to be clarified in future studies.

Recommendation for the treatment of postinfectious dysosmia.

Structured olfactory training should be recommended for postinfectious olfactory dysfunction. If possible, olfactory training should be started within the first year after the onset of dysosmia. However, long-term results of the therapeutic effects are still pending. Furthermore, (additional) drug therapy can be attempted, although higher-grade evidence is lacking today.

(Strong consensus)

2.6.2.2 Posttraumatic dysosmia

Posttraumatic dysosmias are most likely to improve in the first year and may have a worse prognosis after trauma than postinfectious dysosmias (Hummel and Welge-Luessen, 2009b, Reden et al., 2006a, Reden et al., 2012). Prognosis appears to be negatively influenced by age at the time of trauma (> 40 years of age), presence of initial anosmia, and length of preexisting dysosmia (> 15 months) (Jiang et al., 2015, Kuo et al., 2015, London et al., 2008). Whether the severity of traumatic brain injury is associated with prognosis is controversial (Jiang et al., 2015, Kuo et al., 2015, Schofield et al., 2014, Welge-Lüssen et al., 2012). Mild, chronic recurrent traumatic brain injury may also negatively affect olfaction (Vent et al., 2010a). A systematic literature review can be found in Schonfield et al. (Schofield et al., 2014). According to the standard literature, no safe therapeutic option exists for post-traumatic olfactory disorders (Hummel and Welge-Luessen, 2009b), yet various therapeutic strategies have been tested by several research groups.

It has been postulated that the connection of synapses of newly forming axons fails due to fibrosis at the lamina cribrosa (Hummel and Welge-Luessen, 2009b). Based on the aforementioned pathomechanism, the use of a so-called oral cortisone trial was recommended to counteract premature scarring at the lamina cribrosa.

Ikeda et al. (Ikeda et al., 1995) studied 14 patients with posttraumatic anosmia with intravenous T & T olfactometry before and after treatment with topical (n = 12) and systemic corticosteroids (n = 12) (evidence type IV). Improvement in olfaction was reported in one participant after nasal corticosteroid therapy and in 3 of 5 subjects after systemic therapy.

In a study by Fujii et al. (Fujii et al., 2002) an improvement could be achieved in about one third of the patients by regular local dexamethasone injections into the septal mucosa (4mg/0.5 ml, 8 times in intervals of 2 weeks) as well as the administration of vitamin B (over 750 - 1500 µg/d) and adenosine triphosphate (ATP) (300mg/d). This is an open study, the described therapeutic success can only be insufficiently distinguished from the spontaneous remission rate of up to 35% mentioned in the literature (Reden et al., 2006a).

Jiang et al. (Jiang et al., 2010) treated 116 subjects with posttraumatic anosmia in an uncontrolled intervention study with descending doses of prednisolone (initial dose 60 mg/d) for 15 days (evidence type IV). PEA odor threshold was determined analogously to the technique used in the Sniffin' Sticks test. After a mean follow-up of 5.5 months, PEA odor thresholds improved in 16.4% of subjects.

Other studies have anecdotally reported the use of corticosteroids alongside other medications without clear treatment success (Kuo et al., 2015).

Jiang et al. (Jiang et al., 2015) conducted an RCT on 214 subjects with post-traumatic olfactory dysfunction. Study participants were assigned to either therapy with zinc (zinc gluconate 30mg/d for 4 weeks) and prednisolone (initial dose: prednisolone 1 mg/kilogram body weight/d with reduction over 2 weeks) or to zinc or prednisolone alone; 54 subjects did not undergo any therapy (evidence type Ib). Again, olfaction was assessed with a PEA-.

Olfactory threshold measurement (Jiang et al., 2010) analogous to the procedure in the Sniffin' Sticks test. In addition, the olfactory bulb was measured by magnetic resonance imaging. Approximately 2/3 of the participants completed the study and could be included in the final analysis. After a mean follow-up of 5-7 months, 28.2% of the patients treated with prednisolone and zinc improved, 25.7% with zinc and 11.8% with prednisolone as monotherapy and 2.7% without therapy.

In their retrospective case series, Aiba et al. (Aiba et al., 1998) also reported on 95 subjects with posttraumatic olfactory disorders. Four were treated with zinc sulfate (300 mg/d), 70 with the "standard therapy" of vitamin B complex and topical corticosteroids, and 21 with a combination of zinc sulfate and the standard therapy for more than one month (evidence type IV). The success of therapy was assessed on a 7-step ranking scale between "complete recovery" and "worsening" as described above. In the posttraumatic olfactory dysfunction group, there was significant superiority in favor of zinc therapy alone or combined therapy over conventional therapy. Because of the methodology used by Aiba et al, the significance of the above results remains unclear.

The design of the prospective intervention study by Hummel et al. (Hummel et al., 2009a) has already been described in the previous section. The study included 7 subjects with post-traumatic olfactory loss, 5 of whom participated in the olfactory training and 2 of whom did not undergo any therapy. After 12 weeks, there was a significant improvement in the Sniffin' Sticks test in 2 subjects who had undergone olfactory training. In a prospective intervention study, Konstantinidis et al. (2013) examined 23 patients with post-traumatic dysosmia who practiced olfactory training for 16 weeks and compared the results with those of 15 subjects without olfactory training (evidence type IV due to the number of cases). Analogous to the studies of Hummel et al. and Damm et al. the subjects trained twice daily with 4 scents: rose, eucalyptus, lemon and clove (Hummel et al., 2009a, Damm et al., 2013). After 16 weeks of training, olfactory ability improved in the Sniffin' Sticks test (SDI score > 6 points) in 33.2% of the study participants compared to 13% without olfactory training (evidence type IV due to the number of cases).

Other studies of the efficacy of olfactory training in patients with posttraumatic olfactory loss have consistently shown positive effects, but more in the form of low-grade improvements (Bratt et al 2020: open, noncontrolled design, 22 patients, improvement in SDI score at 50% after 1 year; Jiang et al 2019: noncontrolled design, 90 patients, significant improvement in olfactory thresholds after 6 months; see also Ku et al 2022; Langdon et al 2018; Pellegrino et al 2019).

Recommendation for the therapy of post-traumatic dysosmia.

For post-traumatic olfactory disorders, descending therapy with zinc gluconate with or without systemic administration of corticosteroids may be used. Alternatively or complementarily, structured olfactory training may also be recommended. Therapy should be started as soon as possible after the trauma. However, long-term results of the therapy effects or results of larger study populations are still pending.

(Strong consensus)

2.6.2.3 Olfactory disorders in the context of non-sinunasal underlying diseases

The procedure of choice for dysosmias with reference to an underlying disease outside the ENT field is characterized by an interdisciplinary approach and the therapeutic measures are coordinated by the discipline significantly involved (as far as possible evidence-based) (Hummel and Welge-Luessen, 2009b). Based on the current state of knowledge, the prognosis with regard to the olfactory disorder cannot be reliably estimated by initiating therapy for the underlying disease.

Successful accompanying therapy measures are reported only sporadically in the literature. This includes the study by Haehner et al. (Haehner et al., 2013) in subjects with Parkinson's disease and concomitant olfactory dysfunction. In this prospective intervention study, olfactory training in 35 of the 70 participants with the method described by Hummel et al. in 2009 over a period of 12 weeks led to a significant improvement in the Sniffin' Sticks Test score (SDI score) and the olfactory threshold compared to the subjects without olfactory training (evidence type IIb).

Recommendation for non-sinunasal underlying diseases

In the case of olfactory disorders with reference to an underlying disease outside the ENT area, an interdisciplinary approach should be adopted, which is coordinated by the discipline significantly involved.

(Strong consensus)

3 Tasting disorders (dysgeusias)

3.1 Epidemiology

Compared to the frequency of olfactory disorders, taste disorders are observed much less frequently.

Among patients presenting to dedicated centers for olfactory or gustatory disorders, only about 5% actually have a measurable gustatory disorder (Deems et al., 1991). More recent studies even assume only 2% (Merkonidis et al., 2015). Interestingly, unilateral complete ageusia, e.g., after transection of the chorda tympani, is not always subjectively noticed (Grant et al., 1989). In the general population, the frequency of tasting disorders in the sense of hypogeusia is about 5% (however, about 20% of the general population identify only 3 out of 4 clearly suprathreshold offered tasting stimuli: Vennemann et al., 2008), ageusia is found extremely rarely (Welge-Lüssen et al., 2011). Tasting disorders due to self-observation are reported at 19% (Rawal et al., 2016).

Qualitative tasting disorders are frequently complained of. They are found in about 34% of all patients presenting to centers specifically designed for olfactory and gustatory disorders (Deems et al., 1991). Here, tasting stimuli are perceived differently than usual, often as salty or bitter (Fark et al., 2013).

3.2 Terminology on quantitative and qualitative changes of the tasting ability

The ICD code in section R43.- "Disorder of sense of smell and taste" differentiates only 2 diagnoses: R43.2 Parageusia; R43.8 Other unspecified disorder of sense of smell and taste.

However, the ICD systematics should be supplemented or specified for everyday clinical use. Dysgeusia is an umbrella term for qualitative **and** quantitative tasting disorders. Quantitative disorders result from a reduction or enhancement of taste perceptions for sweet, sour, salty, bitter, and umami (see Table 4). Qualitative changes are based on an altered or hallucinatory taste perception of sweet, sour, salty, bitter, and umami (reviews in (Haberland et al. 1999, Bromley et al., 2003; Hummel and Welge-Luessen, 2009b)).

Table 4 Overview of the quantitative classification of the tasting ability

Hypergeusia	Hypersensitivity compared to healthy, young subjects
Normogeusia	Normal sensitivity
Hypogeusia	Decreased sensitivity compared to healthy, young subjects
Ageusie	Very significant impairment of tasting ability, includes both complete loss and the presence of a small amount of residual perception ("functional ageusia"), in which meaningful use in everyday life does not seem possible. **Partial ageusia**: loss of sensitivity to a particular tastant.

Table 5 Overview of qualitative taste disturbances

Parageusia	Altered perception of taste sensations
Phantogeusia	Perception from Taste impressions in absence of a stimulus source (syn.: taste hallucinations)

3.3 Definition and classification of Tasting disorders

Tasting disorders can be divided into peripheral and central nervous disorders based on the site of damage (Welge-Lüssen, 2009, Barlow, 2015). In peripheral nervous tasting disorders, lesions are present in the afferent nerve/axon. Central tasting disorder rarely occurs in isolation and is caused by damage in the brainstem region, thalamus, or may extend to the cortex region (Hummel and Welge-Luessen, 2009b). Furthermore, tasting disorders can be classified according to the triggering cause (e.g., medication side effects, compare Table 5). This

supplementary classification is useful, since it is not always possible to determine the exact location of the damage (e.g., peripheral or central nervous) or to draw therapeutic consequences from it.

3.4 Causes of Tasting disorders

Major causes of tasting disorders include craniocerebral trauma, upper respiratory tract infections, exposure to toxic substances, iatrogenic causes (e.g., surgery or radiation), medications, and burning mouth syndrome (BMS) (reviewed in (Landis and Just, 2010)).

Craniocerebral trauma can cause lesions in areas of the CNS that are important for processing tasting stimuli, e.g., thalamus, brainstem, or the ventral temporal lobe. In addition, fractures of the os temporale or mandibulare may result in injuries to the facial nerve, whereas the glossopharyngeal and vagus nerves are relatively protected deep in the neck (reviewed in (Landis and Just, 2009)).

Restitutio ad integrum is possible (Bull, 1965). For example, in patients with bilateral lesions (Guianand et al., 2010) of the tympanic chorda, recovery of tasting ability was observed after several months. Infections can damage the tasting receptors, innervating nerves, or parts of the CNS (Landis et al., 2005a). The tasting fibers of the facial nerve are most commonly affected here (herpes zoster: Ramsey-Hunt syndrome); they are at risk primarily because of their course through the middle ear.

A variety of drugs can cause taste disturbances, most notably keratolytics, chemotherapeutics, antihistamines, antibiotics, and ACE inhibitors (Douglas et al., 2010; Mortazavi et al., 2018). However, little is known about the mechanisms of injury (Henkin, 1986, Doty et al., 2008). For some drugs, the association with taste disturbances is suggestive, e.g., for those that decrease salivary flow (e.g., anticholinergic drugs such as tricyclic antidepressants), or those that damage the oral mucosa (e.g., antiproliferative drugs such as vincristine).

In contrast, occupationally induced toxic taste disorders appear to be rare (Stuck and Muttray 2008).

Burning mouth syndrome (BMS) is regularly associated with dysgeusia, and a persistent bitter or metallic taste is often reported (reviewed in Grushka et al., 2003; Eliav et al., 2007; Klasser et al., 2016). Other symptoms include dry mouth and thirst. Often, the burning sensation increases throughout the day. It occurs most frequently in post-menopausal women - but is by no means always amenable to hormonal replacement therapy. In about half of cases, spontaneous partial remission occurs within 6 years of onset. Etiologically, psychological (e.g. depression), hormonal (estrogen level changes) and nutritional causes (vitamin B1, 2, 6 or zinc deficiency) have been discussed.

Other causes of taste disorders include tumors, bulimia, hypothyroidism, Cushing's syndrome (decrease in taste sensitivity with increase in plasma levels of glucocorticoids), diabetes mellitus, liver and kidney failure, or gastroesophageal reflux (Adamoet al., 2023). An additional factor for dysgeusia is considered to be poor oral hygiene - but on the other hand, the use of mouthwash, for example, can also lead to taste disorders (Landis and Just, 2010, Su and Grushka, 2013).

3.5 Basic diagnostics for tasting disorders

Basic diagnostics include general and specific anamnesis (triggering events, temporal development, concomitant symptoms, relevant diseases / operations / medications / noxae), an ENT status, endoscopy of the nose / nasopharynx, magnifying laryngoscopy, palpation of the tongue (Welge-Luessen et al., 2013), an orienting olfactory examination (Hummel et al., 2001, Hummel et al., 2007), and differential quantitative determination of overall or local tasting ability. The special medical history includes questioning about recent dental or oral surgical therapies, known kidney diseases, diabetes, gastroesophageal reflux disease or other systemic diseases, as well as upper respiratory tract infections experienced immediately before. In addition, the medical history is directed towards head trauma, psychiatric and neurodegenerative diseases and after mouth/ tongue burning (see above, glossodynia, "burning-mouth-syndrome") (Schuster et al 2009, Hummel 2009b).

3.6 Examination procedure for Tasting disorders

Although the most common tasting disorders are qualitative in nature, such as parageusia or phantogeusia, many clinical taste tests only examine quantitatively impaired tasting ability (Müller et al., 2007). Usually, the perception of sweet, sour, salty, and bitter is assessed. Testing sensitivity to umami has not yet gained acceptance in clinical practice, primarily because only a portion of the general population is able to detect umami (Zhu and Hummel 2022; Cecchini et al. 2019).

Usually, the detection thresholds and the identification ability of suprathreshold tastants are determined and, possibly, intensity estimates are initiated. The taste tests are used to test the overall tasting ability globally as "whole mouth testing" or to test the regional tasting ability of individual gustatory areas (Hummel and Welge-Luessen, 2009b).

Table 6 Causes and classification of taste disorders

Peripheral nervous damage	This subheading includes all damage to peripheral nerves involved in taste sensation (facial and intermediary, glossopharyngeal and vagus nerves). These are very often postoperative injuries (Hamada *et al.*, 2002; Hotta *et al.*, 2002; Landis *et al.*, 2005; Tomofuji *et al.*, 2005; Nin *et al.*, 2006; Landis *et al.*, 2007; Mueller *et al.*, 2007; Sahu *et al.*, 2008; Landis & Guinand, 2009; Heiser *et al.*, 2010, 2012). Examples include lesion of cranial nerves VII, IX, X, e.g., after/in surgery of the ears (Landis et al., 2005), tonsillectomy (Mueller et al., 2007, Windfuhr et al., 2010), neck dissection, tumors (Ribas et al., 2012), or other causes such as skull base fractures (Renzi et al., 2002), carotid dissection or neuritis (Dahlslett et al., 2012).
Central nervous damage	Tasting disorders caused by either CNS lesions (e.g., tumor, MS, infarction, trauma) or neurodegenerative CNS diseases (Heckmann *et al.*, 2005; Landis *et al.,* 2006; Onoda *et al.*, 2012).
Drug-toxic, radiotherapeutic, or chemotherapeutic side effects.	In the group of drug-toxicity-induced side effects, radio- and chemotherapy are among the best known causes (Sandow et al., 2006; Mirza et al., 2008; Steinbach et al., 2009, e.g., damage to epithelial sensory cells and/or the taste buds in the course of radiotherapy. In principle, however, any administered substance can lead to taste disturbances, with some substance classes leading to taste disturbances more frequently (Bromley & Doty, 2003; Doty & Haxel, 2005).
Occurring in the context of systemic, metabolic, or deficiency diseases.	Vitamin/zinc deficiency and other deficiency symptoms. Systemic diseases that alter salivary flow can also lead to tasting disorders. At the same time, a tasting disorder can also be the initial or accompanying symptom of a systemic disease (Petzold *et al.*, 2003; Nakazato *et al.*, 2008; Chabwine *et al.*, 2014).
Post-infectious	Tasting disorders, which are due to infectious events
Idiopathic, age-related or in the context of Burning Mouth Syndrome occurring taste disorders.	Exclusion diagnoses (Fark *et al.*, 2013).

3.6.1 Psychophysical testing of the global tasting ability

3.6.1.1 Screening of the global smear function

A suitable screening test is the oral application of sweet, sour, salty and bitter tastants, each in a suprathreshold concentration, which the subject is to recognize correctly. In a screening taste test, a 10% sucrose solution, a 5% citric acid solution, a 7.5% sodium chloride solution, and a 0.05% quinine hydrochloride solution are sprayed into the mouth one or more times (approximately 60 µl per spray) (Welge-Lüssen and Hummel, 2009). The subject is asked to identify after each tasting quality tested.

The **three-drop method** (Henkin et al., 1963) is clinically popular and allows the detection thresholds for sweet, sour, salty, and bitter to be determined. The patient:s must recognize the one with tastant from three drops and correctly name the tasting quality. The initially subthreshold tastant concentration is increased until the patient correctly names the same concentration of a tastant quality at least twice in three trials (Gudziol and Hummel, 2007; see also Fjaeldstad et al. 2019).

In contrast to the ascending three-drop method, near-threshold and suprathreshold tasting solutions can also be pseudorandomized as a **one-drop test** according to a fixed sequence. With this methodology, a gustatory index is usually determined by summation of all detected concentration levels of the 4 tasting qualities (overview in Richter, 2002). It is preferred by the test persons. Fatigue symptoms occur only rarely. However, the gustatory index has the disadvantage that it is not initially obvious which tasting quality is recognized more poorly.

3.6.1.2 Verification of the ability to identify

The **verification of the identification ability** by means of suprathreshold tastants is a frequently used test method. Different working groups offer different numbers of tastant concentrations for each tasting quality: 15,
6 or 4 (Grant et al., 1989, Ahne et al., 2000, Glöckner, 2000). The application of the tastants occurs both in liquid form (see above) and in solid form (e.g. impregnated tasting strips, "taste-strips" (Tomita et al., 1986, Mueller et al., 2003,

Smutzer et al., 2008, Landis et al., 2009, Mueller et al. 2011). The tests are either ascending or pseudorandomized.

3.6.1.3 Intensity estimates

Another test variant for checking the tasting ability uses **intensity estimates of** the offered tasting concentrations either according to a scale from weak to strong or also in comparison with variable loudnesses of a 1000 Hz tone (Bartoshuk, 1989). However, a number of subjective factors may influence the test result.

3.6.2 Psychophysical testing of the regional tasting ability

The testing of regional tasting ability is mainly used in cases of suspected regional tasting impairment, especially as a result of nervous damage such as a lesion of the chorda tympani or the glossopharyngeal nerve.

As screening, highly concentrated tasting solutions can be applied locally, brushed and identified (Wardrop et al., 1989, Nishimoto et al., 1996). During testing, the patient:s must stick out their tongue slightly and show on a board what taste perception they have. The tongue should be held very still while doing this. One should not speak during this process so that the applied tastants do not spread over the gustatory area to be tested.

For quantitative testing of regional tasting ability, either tasting solutions or dry filter paper strips impregnated with tasting material ("taste- strips") can be used. The tasting solutions can either be brushed on with a cotton swab (Bartoshuk, 1989) or applied with an ear probe according to Tröltsch (Arbeitsgemeinschaft Klinische Olfaktologie und Gustologie der Gesellschaft für Oto-Rhino- Laryngologie und cervikofaziale Chirurgie der DDR, 1980) or with filter paper discs. "Taste-strips" are filter paper strips impregnated with tasting substances, which can be used to quantitatively and qualitatively test the regional tasting ability at least in the supply area of the chorda tympani (Mueller et al., 2007, Tolbert, 1998, Landis et al., 2009). Among the more common methods such as the Taste strips (Fjaeldstad et al.,

2018) as well as to the 3-drop method (Pingel et al., 2010), studies on reliability and validity are available.

3.6.2.1 **Electrogustometry**

The fastest and simplest method for checking the side difference of the same gustatory areas is electrogustometry (Haberland et al., 1974). This method is used to determine the electrical perception threshold. Stimulation is monopolar (anodal) or bipolar (coaxial) with battery current between 1.5 µA and 400 µA (Tomita and Ikeda, 2002). The stimulus scaling is usually designed logarithmically and is then referred to as the gustatory decibel. The electrogustometer (e.g., Sensonics Inc., Haddon Heights, NJ, USA) can be used to increase the stimulus intensity in 2 dB steps from -6 dB (1.5 µA) to 40 dB (300 µA). Perceptual thresholds for electrical taste vary widely among individuals and are different across gustatory areas (norm values in Pavlidis et al., 2021). It is important to compare intraindividually both sides of the same gustatory area of the supply area of the chorda tympani, the
petrosal major nerve or glossopharyngeal nerve. A lateral difference of > 7 dB is considered pathological (Roseburg and Fikentscher, 1984). The advantage of electrogustometry is the rapid detection of a nerve lesion and the possibility to measure the gustatory components of the
glossopharyngeal nerve. A disadvantage of electrogustometry is that it may not be possible to detect taste disorders that affect only individual taste qualities. Furthermore, in the case of suprathreshold stimulation, sometimes no correlation is found between electrogustometric measurements and measurements using adequate tasting stimuli (Murphy et al., 1995) (but see also (Just et al., 2005)).

3.6.4 Gustatory evoked potentials (GEP)

Analogous to olfactory evoked potentials, GEP can be recorded at specialized centers. Gustatory evoked potentials, however, have no place in routine diagnostics of taste disorders and are largely reserved for scientific questions. In the derivation of GEP, the taste receptors of the tongue are stimulated using aqueous solutions. In this process, the liquids are atomized at low pressure and sprayed over a large area on the tongue. After a definable number of water pulses, one or more taste pulses occur. Almost immediate rinsing with water results in both a short rise time of the stimulus and a rapid fall. By heating the liquids to body temperature, thermal irritation of the tongue can be avoided. In this way, it is possible to derive purely gustatory evoked potentials. (Reviews in (Ikui, 2002; Hummel et al., 2010; Iannilli et al., 2014)). To what extent the combination of gustatory evoked potentials in combination with MRI or functional MRI will provide new insights in the coming years remains to be seen.

3.6.5 Further diagnostics

The indication for further diagnostics requires a case-by-case decision. Further diagnostics include imaging examinations of the neurocranium or the oral and cervical region by means of CT or MRI (e.g., see also recommendations of the DRG Head and Neck Radiology Working Group), as well as the recording of saliva volume, measurement of the number of taste buds, determination of vitamin A, vitamin B12, folic acid, zinc, creatinine, and iron in serum, and, if necessary, virus serology, blood glucose/HbA1c, and, if necessary, sample excision (Hummel and Welge-Luessen, 2009b). Contact endoscopy is available to detect morphological changes (Just et al., 2006). After staining the tongue epithelium with methylene blue, the tongue epithelium, especially the fungiform papillae, is examined using endoscopic optics with up to 150x magnification (Nuessle et al. 2015). Contact endoscopy is rarely offered in the investigation of taste disorders and when it is, it is offered in distinctly specialized centers (Just et al. 2006, Pavlidis et al., 2015). Histological examinations of papillae after biopsies have not proven to be of diagnostic value in clinical practice (Zhu and Hummel 2022).

Recommendation for the use of psychophysical testing procedures in tasting disorders.

For routine diagnostics, global testing with suprathreshold tasting solutions for sweet, sour, salty and bitter as spray or drops is suitable. Suprathreshold testing should only be used as a screening method. Also suitable for routine diagnostics is the 3-drop test method (Henkin et al., 1963), which can be used to determine the tasting threshold (Gudziol et al., 2007). Taste strips (Mueller et al., 2003, Nordin et al., 2007) can be used to test regional tasting ability and have been successfully used in several clinical studies (Landis et al., 2009, Hummel and Welge-Luessen, 2009b). For higher grade recommendations, further studies on test methodology are needed (with equivalence tests or Bland-Altman diagrams).

(Strong consensus)

3.7 Therapy of Tasting disorders

Detailed and expert counseling of the affected person represents an elementary component of the therapy. Nutritional counseling should be considered, especially in cases of weight loss due to tasting disorders. Measures such as mucosal care (sialagoga/saliva substitute), stimulation of residual gustatory function (e.g., by re-seasoning), and noxious elimination (e.g., nicotine abstinence) can have a supportive effect.

The important key to therapy is to make the diagnosis as accurately as possible. The tasting system has an exceptionally high tendency to spontaneous recovery. However, recovery rarely occurs within a few weeks; it usually takes months or even years. It also seems to make sense to re-admit patients at regular intervals and, if necessary, to document their progress with psychophysical taste tests.

If a drug-induced tasting disorder is suspected, the focus is on discontinuation or replacement (as far as medically possible). In the majority of cases, the tasting ability recovers spontaneously. In the case of drug-induced zinc deficiency (e.g. drugs with a sulfhydryl group such as penicillamine), zinc and sometimes also selenium substitution can alleviate the taste problem.

improve. In the case of taste disorders in which deficiency symptoms are suspected, the initiation of substitution therapy is recommended after appropriate diagnostics. In the case of nutrition-related taste disorders, the causes are often deficiencies that can be remedied by nutritional counseling (e.g., abandoning a diet that is too one-sided). In case of suspected taste disorders in the context of an underlying disease (e.g. neurodegenerative diseases or diabetes mellitus), an interdisciplinary treatment is carried out after the diagnosis has been confirmed (reviews e.g. in (Doty et al., 2008, Hummel and Welge-Luessen, 2009b)). In the case of dysgeusia associated with systemic diseases, the taste disorder regularly improves after initiation/optimization of the therapy of the underlying disease.

In the case of particularly high suffering pressure of the affected person due to qualitative taste disturbances

among other things also tried to rinse the oral cavity with 2% lidocaine solution, in the oral cavity 1

- Apply 5 sprays of 10% lidocaine or apply a 2% lidocaine gel to the tongue (Formaker et al., 1998). There are few proven options for the specific therapy of taste disorders.

3.7.1 Zinc

Although zinc administration is frequently used in daily routine, its efficacy in taste disorders is controversial (Henkin et al., 1976, Stoll and Oepen, 1994). However, recent double-blind RCTs suggest that zinc (e.g., zinc gluconate 140 mg/d for 4 months) can improve symptoms at least in idiopathic dysgeusia and renal zinc deficiency (Heckmann et al., 2005, Mahajan et al., 1980, Mahajan et al., 1982, Nagraj et al., 2014, Sakagami et al., 2009, Sakai et al., 2002). In 2017, Nagraj et al. conducted a systematic literature review on the therapy of tasting disorders, which was published in the Cochrane Library (Kumbargere Nagraj et al., 2017). All parallel and cross-over RCTs were included in the aforementioned literature review. Other inclusion criteria were quantitative and qualitative tasting disorders. Age, gender, ethnicity, and occupation were not considered. Exclusion criteria were tumors of the tongue, soft palate, or oropharynx; radiochemotherapy; thrush; stomatitis; dry mouth; endocrinologic and neurodegenerative diseases. Kumbargere Nagraj et al. (2017) were ultimately able to evaluate 9 studies, in which zinc was used in 8 studies in a total of 529 subjects with

taste disorders compared to placebo. In the analysis, both the heterogeneity of the included subjects and the methodology used to measure treatment effects were problematic. Kumbargere Nagraj et al. (2017) concluded that, based on the study evidence, there would be insufficient evidence to suggest an improvement in self-assessment of tasting ability with zinc supplementation in idiopathic tasting disorders and tasting disorders associated with zinc deficiency diseases. With "moderate" evidence, a general improvement of the tasting ability in the objectifying test by zinc substitution in the aforementioned patient groups was assumed. In summary, Kumbargere Nagraj et al. (2017) assessed the level of evidence from the literature available to date for the therapeutic approach of zinc substitution in idiopathic dysgeusia and renal zinc deficiency as very low (see also Doty 2019, Neta et al. 2021, Braud and Boucher 2020).

3.7.2 Other therapeutic approaches

A controlled RCT (Mattes et al., 2004) with Ginkgo biloba showed no efficacy compared with placebo (no treatment effect, evidence type IIb). Brandt et al. (2008) conducted a single-blind placebo-controlled RCT on the efficacy of acupuncture for idiopathic tasting disorder (verum group: 10 to 15 treatments with needle acupuncture, control group: placebo laser acupuncture n = 37, evidence type IIb). The verum group improved significantly in the tasting strip test and symptom self-assessment compared to the control group.

In addition, numerous positive treatment effects have been described in the literature at low levels of evidence in case reports or non-controlled studies: Administration of biotin (case report, evidence type IV, (Greenway et al., 2011)), alpha lipoic acid (controlled intervention study, n = 44, evidence type III (Femiano et al., 2002)), salivary stimulation with glutamate (case series, n = 44, evidence type IV, (Sasano et al., 2010), haloperidol and thioridazine (case report, evidence type IV, (Henkin et al., 2000)), theophylline (case series, n = 10, evidence type IV, (Henkin et al., 2012a)), transcranial magnetic stimulation for phantgeusia (case series, n = 17, evidence type IV, (Henkin et al., 2011)), stimulation with ice cubes (case report, evidence type IV, (Fujiyama et al., 2010)), or administration of miracle berry (case series, n = 8, evidence type IV, (Wilken et al., 2012)).

Other studies with low levels of evidence are available for esomeprazole, L-thyroxine, bethanechol, oral glutamine, delta-9-tetrahydrocannabinol, alpha-lipoic acid, artificial saliva, pilocarpine, local anesthesia, and improved oral hygiene (see summary in Braud and Boucher, 2020).

Recommendation for the therapy of taste disorders

Expert counseling of the affected person should be an elementary part of the therapy (if necessary also with nutritional counseling). The variety of therapeutic measures proposed for the treatment of tasting disorders is contrasted by only a low level of evidence from the literature. The best evaluated therapeutic approach is zinc administration in idiopathic tasting disorders. From a clinical perspective, a therapeutic trial of zinc can be attempted in idiopathic tasting disorders or in the setting of zinc deficiency. If drug side effects are suspected, withdrawal or switching measures should be taken. Tasting disorders in the context of dermatological, internal and neurological underlying diseases regularly require an interdisciplinary approach, therapeutic measures or

-The subject significantly involved should coordinate the trials.

(Strong consensus)

4 Literature

Abdelazim MH et al (2022), Effect of intra-nasal nitrilotriacetic acid trisodium salt in lowering elevated calcium cations and improving olfactory dysfunction in COVID-19 patients. Eur Arch Otorhinolaryngol 279: 4651.

Abdelazim MH, Abdelazim AH, Moneir W (2022) The effect of intra-nasal tetra sodium pyrophosphate on decreasing elevated nasal calcium and improving olfactory function post COVID-19: a randomized controlled trial. Allergy Asthma Clin Immunol 18: 67. Abolmaali N, Gudziol V, Hummel T (2008) Pathology of the olfactory nerve. Neuroimaging Clin N Am 18:233-242.

Ackerman BH, N. Kasbekar (1997) Disturbances of taste and smell induced by drugs. Pharmacotherapy 17: 482-496

Adamo D et al. (2023) Burning mouth syndrome: analysis of diagnostic delay in 500 patients. Oral Dis.

Ahne G, Erras A, Hummel T, Kobal G (2000) Assessment of gustatory function by means of tasting tablets. Laryngoscope 110: 1396-1401

Aiba T, Sugiura M, Mori J et al. (1998) Effect of zinc sulfate on sensorineural olfactory disorder. Acta Oto-Laryngologica:202-204.

Alobid I, Benitez P, Pujols L et al. (2006) Severe nasal polyposis and its impact on quality of life. The effect of a short course of oral steroids followed by long-term intranasal steroid treatment. Rhinology 44(1):8-13.

Altundag A, Cayonu M, Kayabasoglu G et al. (2015) Modified olfactory training in patients with postinfectious olfactory loss. Laryngoscope 125(8):1763-1766.

Amoore J. (1986) Effects of chemical exposure on olfaction in humans. In: Barrow C, Craig S, eds. Toxicology of the nasal passages. Washington: Hemisphere Publ. Corp.,155-90

Anzinger A, Albrecht J, Kopietz R et al. (2009) Effects of laserneedle acupuncture on olfactory sensitivity of healthy human subjects: a placebo-controlled, double-blinded, randomized trial. Rhinology 47(2):153-159.

Arbeitsgemeinschaft Klinische Olfaktologie und Gustologie der Gesellschaft für Oto-Rhino-Laryngologie und cervico-facial Chirurgie der DDR (1980) Recommendations for the examination of olfaction and gustation. ENT Practice 5: 62-67

Bachert C, Borchard U, Wedi.B. et al (2003) Allergic rhinoconjunctivitis. Allergo Journal 12:182- 194.

Bachert, Claus, Ana R. Sousa, Valerie J. Lund, Glenis K. Scadding, Philippe Gevaert, Shuaib Nasser, Stephen R. Durham, et al. 2017. "Reduced Need for Surgery in Severe Nasal Polyposis with Mepolizumab: Randomized Trial." Journal of Allergy and Clinical Immunology 140 (4): 1024-1031.e14. https://doi.org/10.1016/j.jaci.2017.05.044.

Bachert C, Zhang N, Cavaliere C, Weiping W, Gevaert E, Krysko O (2020) Biologics for chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 145: 725-739.

Bachmann G, Hommel G, Michel O (2000) Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. Eur Arch Otorhinolaryngol 257(10):537-541.

Bajaj S et al (2012) Oral manifestations in type-2 diabetes and related complications. Indian J Endocrinol Metab 16: 777-779.

Banov CH, Lieberman P (2001) Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. Ann Allergy Asthma Immunol 86(1):28-35.

Baraniuk JN, Merck SJ (2009) New concepts of neural regulation in human nasal mucosa. Acta Clin Croat 48(1):65-73.

Barlow LA (2015) Progress and renewal in gustation: new insights into taste bud development. Development 142: 3620-3629

Bartoshuk LM (1989) Clinical evaluation of the sense of taste. Ear Nose Throat J 68: 331-337

Bartoshuk LM, Catalanotto FC, Scott AE, Solomon GM (1989) Spatial taste losses associated with head trauma, upper respiratory infection and nasal symptoms. Chem Senses 14: 684

Bednár M. Anosmia and influenza, A rhinological contribution to the differential diagnosis of colds. 48 ed. 1930.

Benitez P, Alobid I, de Haro J et al. (2006) A short course of oral prednisone followed by intranasal budesonide is an effective treatment of severe nasal polyps. Laryngoscope 116(5):770-775.

Berg D et al. (2013) The PRIPS study: screening battery for subjects at risk for Parkinson's disease. Eur J Neurol 20:102-108.

Bergasa NV (1998) Hypothesis: Taste disorders in patients with liver disease may be moderated in the brain: potential mechanisms for a central phenomenon. Am J Gastroenterol 93(8): 1209-1210.

Berges-Gimeno MP, Simon RA, Stevenson DD (2003a) Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol 90(3):338-341.

Bernstein JA (2007) Azelastine hydrochloride: a review of pharmacology, pharmacokinetics, clinical efficacy and tolerability. Curr Med Res Opin 23(10):2441-2452.

Bernstein JA (2013a) Characterizing rhinitis subtypes. Am J Rhinol Allergy 27(6):457-460.

Bernstein JA (2013c) Nonallergic rhinitis: therapeutic options. Curr Opin Allergy Clin Immunol 13(4):410-416.

Bernstein JA, Davis BP, Picard JK, Cooper JP, Zheng S, Levin LS (2011a) A randomized, double-blind, parallel trial comparing capsaicin nasal spray with placebo in subjects with a significant component of nonallergic rhinitis. Ann Allergy Asthma Immunol 107(2):171-178.

Bernstein JA, Hastings L, Boespflug EL, Allendorfer JB, Lamy M, Eliassen JC (2011b) Alteration of brain activation patterns in nonallergic rhinitis patients using functional magnetic resonance imaging before and after treatment with intranasal azelastine. Ann Allergy Asthma Immunol 106(6):527-532.

Bernstein JA, Prenner B, Ferguson BJ, Portnoy J, Wheeler WJ, Sacks HJ (2009) Double-blind, placebo-controlled trial of reformulated azelastine nasal spray in patients with seasonal allergic rhinitis. Am J Rhinol Allergy 23(5):512-517.

Bernstein JA, Singh U (2015) Neural abnormalities in nonallergic rhinitis. Curr Allergy Asthma Rep 15(4):18.

Bitter T, Siegert F, Gudziol H et al. (2011) Gray matter alterations in parosmia. Neuroscience 177:177-182.

Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1(8476):307-310.

Blau JN, Solomon F. (1985) Smell and other sensory disturbances in migraine. J Neurol. 232(5):275-276.

Blom HM, van Rijswijk JB, Garrelds IM, Mulder PG, Timmermans T, Gerth vW (1997) Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. Clin Exp Allergy 27(7):796-801.

Blomqvist EH, Lundblad L, Anggard A, Haraldsson PO, Stjarne P (2001) A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis. J Allergy Clin Immunol 107(2):224-228.

Blomqvist EH, Lundblad L, Bergstedt H, Stjarne P (2009) A randomized prospective study comparing medical and medical-surgical treatment of nasal polyposis by CT. Acta Otolaryngol 129(5):545-549.

Boscolo-Rizzo P et al. (2022) Coronavirus disease 2019 (COVID-19)-related smell and taste impairment with widespread diffusion of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) Omicron variant. Int Forum Allergy Rhinol 12: 1273-1281.

Boesveldt S, Lindau ST, McClintock MK, Hummel T, Lundstrom JN (2011) Gustatory and olfactory dysfunction in older adults: a national probability study. Rhinology 49:324-330.

Bousquet J et al (2008) Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 63 Suppl 86:8-160.

Bousquet J et al. (2012) Allergic rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol 130(5):1049-1062.

Brämerson A, Johansson L, Ek L, Nordin S, Bende M (2004) Prevalence of olfactory dysfunction: the Skövde population-based study. Laryngoscope 114:733-737.

Brandt H, Hauswald B, Langer H, Gleditsch J, Zahnert T (2008) Efficacy of acupuncture in the therapy of idiopathic tasting disorders. Dt Zeitschr Akupunktur 51:24-31.

Brann DH et al (2020) Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 6: eabc5801

Bratt M, Moen KG, Nordgård, S, Helvik AS, Skandsen T (2020) Treatment of posttraumatic olfactory dysfunction with corticosteroids and olfactory training. Acta Otolaryngol 140: 761-767.

Braud A, Boucher Y (2020) Taste disorder's management: a systematic review. Clin Oral Investig, 24: 1889-1908.

Bromley SM, Doty RL (2003) Clinical disorders affecting taste: evaluation and management. In: Doty RL (ed.). Handbook of olfaction and gustation, Marcel Dekker New York, Basel, 935-957.

Bronsky EA, Druce H, Findlay SR et al (1995) A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. J Allergy Clin Immunol 95(5 Pt 2):1117-1122.

Bull TR (1965) Taste and the chorda tympani. J Larnygol Otol 79: 479-493

Cain WS, Gent J, Catalanotto FA, Goodspeed RB (1983) Clinical evaluation of olfaction. Am J Otolaryngol 4(4):252-256.

Cain WS, Gent JF, Goodspeed RB, Leonard G (1988) Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center (CCCRC). Laryngoscope 98:83-88.

Cardesin A, Alobid I, Benitez P, Sierra E, de Haro J, Bernal-Sprekelsen M, Picado C, Mullol J (2006) Barcelona Smell Test-24 (BAST-24): validation and odor characteristics in the healthy Spanish population. Rhinology 44:83-89.

Cecchini MP, Fasano A, Boschi F, Osculati F, Tinazzi M.(2015) Taste in Parkinson's disease. J Neurol 262(4): 806-13.

Cecchini MP, Knaapila A, Hoffmann E, Boschi F, Hummel T, Iannilli E (2019) A cross-cultural survey of umami familiarity in European countries. Food Qual Pref 74: 172-178.

Chabwine JN, Tschirren MV, Zekeridou A, Landis BN, Kuntzer T. (2014). Sweet taste loss in myasthenia gravis: more than a coincidence? Orphanet J Rare Dis 9, 50.

Chang H, Han DH, Mo JH et al (2009) Early compliance and efficacy of sublingual immunotherapy in patients with allergic rhinitis for house dust mites. Clin Exp Otorhinolaryngol 2(3):136-140.

Cheng J, Yang XN, Liu X, Zhang SP (2006) Capsaicin for allergic rhinitis in adults. Cochrane Database Syst Rev(2):CD004460.

Chong LY, Head K, Hopkins C et al (2016) Saline irrigation for chronic rhinosinusitis. Cochrane Database Syst Rev 4:CD011995.

Ciprandi G (2004) Treatment of nonallergic perennial rhinitis. Allergy 59 Suppl 76:16-22.

Cohen J. Statistical power analysis for the behavioral sciences. New York: Lawrence Erlbaum Associates Inc, 1988.

Comert S, Celebioglu E, Yucel T et al. (2013) Aspirin 300 mg/day is effective for treating aspirin-exacerbated respiratory disease. Allergy 68(11):1443-1451.

Conley DB, Robinson AM, Shinners MJ, Kern RC (2003) Age-related olfactory dysfunction: cellular and molecular characterization in the rat. Am J Rhinol 17(3):169-175.

Conti MZ et al. (2013) Odor identification deficit predicts clinical conversion from mild cognitive impairment to dementia due to Alzheimer's disease. Arch Clin Neuropsychol 28(5):391-399.

Costanzo RM, Becker DP (1986) Smell and taste disorders in head injury and neurosurgery patients. In: Meiselman HL, Rivlin RS (eds) Clinical measurements of taste and smell, MacMillian New York, 565- 578.

Cowart BJ (1989) Relationships between taste and smell across the adult life span. Ann NY Acad Sci 561: 39-55.

Croy I, Hoffmann H, Philpott C, Rombaux P, Welge-Luessen A, Vodicka J, Konstantinidis I, Morera E, Hummel T (2014) Retronasal testing of olfactory function: an investigation and comparison in seven countries. Eur Arch Otorhinolaryngol 271:1087-1095.

Croy I, Hummel T, Pade A, Pade J (2010) Quality of life following nasal surgery. Laryngoscope 120(4):826-831.

Croy I, Lange K, Krone F, Negoias S, Seo HS, Hummel T (2009) Comparison between odor thresholds for phenyl ethyl alcohol and butanol. Chem Senses 34:523-527.

Croy I, Olgun S, Mueller L, Schmidt A, Muench M, Hummel C, Gisselmann G, Hatt H, Hummel T (2015) Peripheral adaptive filtering in human olfaction? Three studies on prevalence and effects of olfactory training in specific anosmia in more than 1600 participants. Cortex 73:180-187.

Croy I, Yarina S, Hummel T (2013) Enhanced parosmia and phantosmia in patients with severe depression. Psychol Med 43(11):2460-2464.

D'Ascanio L, Vitelli F, Cingolani C, Maranzano M, Brenner MJ, Di Stadio A (2021) Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with palmitoylethanolamide and luteolin": preliminary results. Eur Rev Med Pharmacol Sci 25: 4156-4162.

Dahlen B, Nizankowska E, Szczeklik A et al (1998) Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. Am J Respir Crit Care Med 157(4 Pt 1):1187-1194.

Dahlslett SB, Goektas O, Schmidt F, Harms L, Olze H, Fleiner F (2012) Psychophysiological and electrophysiological testing of olfactory and gustatory function in patients with multiple sclerosis. Eur Arch Otorhinolaryngol 269: 1163-1169.

Dalgic A, Dinc ME, Ulusoy S, Dizdar D, Is A, Topak M (2017) Comparison of the effects of nasal steroids and montelukast on olfactory functions in patients with allergic rhinitis. Eur Ann Otorhinolaryngol Head Neck Dis 134(4):213-216.

Damm M (2006) Idiopathic rhinitis. Laryngorhinootologie 85(5):361-377.

Damm M (2007) Diagnosis of olfactory disorders-standards and research. Laryngorhinootologie 86(8):565-572.

Damm M, Eckel HE, Jungehulsing M, Hummel T (2003) Olfactory changes at threshold and suprathreshold levels following septoplasty with partial inferior turbinectomy. Ann Otol Rhinol Laryngol 112(1):91-97.

Damm M, Jungehulsing M, Eckel HE, Schmidt M, Theissen P (1999) Effects of systemic steroid treatment in chronic polypoid rhinosinusitis evaluated with magnetic resonance imaging. Otolaryngology-Head and Neck Surgery 120(4):517-523.

Damm M, Leung RM, Kern RC. Sinonasal olfactory disorders. In: Welge-Lüssen A, Hummel T, editors. Management of smell and taste disorders. Stuttgart, New York: Thieme, 2014: 76-90.

Damm M, Pikart LK, Reimann H et al (2013) Olfactory training is helpful in postinfectious olfactory loss: A randomized, controlled, multicenter study. Laryngoscope.

Damm M, Quante G, Jungehuelsing M, Stennert E (2002a) Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. Laryngoscope 112(2):310-315.

Damm M, Temmel A, Welge-Lüssen A et al. (2004) Olfactory disorders. Epidemiology and therapy in Germany, Austria, and Switzerland. HNO 52(2):112-120.

Damm M, Vent J, Schmidt M et al. (2002b) Intranasal volume and olfactory function. Chemical Senses 27(9):831-839.

Damm M. Sinunasal dysosmias. In: Hummel T, Welge-Lüssen A, editors. Olfactory and gustatory disorders- physiology, pathophysiology and therapeutic approaches. Stuttgart, New York: Thieme Verlag, 2009.

Davidson TM, Murphy C (1997) Rapid clinical evaluation of anosmia. The alcohol sniff test. Arch Otolaryngol Head Neck Surg 123:591-594.

Deems DA et al (1991) Smell and taste disorders: a study of 750 patients from the University of Pennsylvania Smell and Taste Center. Arch. Otorhinolaryngol. Head Neck Surg 117: 519-528

Deems DA, Yen DM, Kreshak A, Doty RL (1996) Spontaneous resolution of dysgeusia. Arch Otolaryngol Head Neck Surg 122: 961-963.

Delank KW (1998) Subjective and objective methods for assessing olfactory function. HNO 46:W182-190.

Delank KW, Fechner G (1996) On the pathophysiology of posttraumatic olfactory disorders. Laryngol Rhinol Otol 75:154-159.

Dexeus S, Cararach M, Dexeus D (2002) The role of colposcopy in modern gynecology. Eur J Gynaecol Oncol 23: 269-277.

Doty RL (1995) The Smell Identification Test™ Administration Manual. 3rd edition. Haddon Heights, New Jersey: Sensonics, Inc.

Doty RL (2009) The olfactory system and its disorders. Semin Neurol 29:74-81.

Doty RL, Marcus A, Lee WW (1996) Development of the 12-item cross-cultural smell identification test (CC-SIT). Laryngoscope 106:353-356.

Doty RL & Haxel BR. (2005). Objective assessment of terbinafine-induced taste loss. Laryngoscope 115, 2035-2037.

Doty RL, Hawkes CH (2019) Chemosensory dysfunction in neurodegenerative diseases. Handb Clin Neurol 164:325-360.

Doty RL, Shah M, Bromley SM (2008) Drug-induced taste disorders. Drug Saf 31.

Doty RL, Shaman P, Dann M (1984) Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol Behav 32:489-502.

Doty RL (2019) Treatments for smell and taste disorders: a critical review. Handb Clin Neurol, 164, 455- 479.

Doty RL (2022) Olfactory dysfunction in COVID-19: pathology and long-term implications for brain health. Trends Mol Med 28(9):781-794

Douglass R, Heckman G (2010) Drug-related taste disturbance: a contributing factor in geriatric syndromes. Can Fam Physician 56: 1142-7.

Drake-Lee A, Ruckley R, Parker A (2002) Occupational rhinitis: a poorly diagnosed condition. J Laryngol Otol 116(8):580-585.

Drews T, Hummel T (2016) Treatment strategies for smell loss. Curr Otorhinolaryngol Rep 4: 122-129.

Drews T, Hummel T, Rochlitzer B, Hauswald B, Hähner A (2021) Acupuncture is associated with a positive effect on odour discrimination in patients with postinfectious odour loss-a controlled prospective study. Eur Arch Otorhinolaryngol 279(3): 1329-1334.

Duff K, McCaffrey RJ, Solomon GS (2002) The Pocket Smell Test: successfully discriminating probable Alzheimer's dementia from vascular dementia and major depression. J Neuropsychiatry Clin Neurosci 14:197-201.

Duncan HJ, Seiden AM (1995a) Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection Arch Otolaryngol Head Neck Surg 121(10):1183-1187.

Dupont WD, Plummer WD, Jr (1990) Power and sample size calculations. A review and computer program. Control Clin Trials 11(2):116-128.

Eliav E et al (2007). Evidence of chorda tympani dysfunction in patients with burning mouth syndrome. JADA 138: 628-633

Fark T, Hummel C, Hahner A, Nin T, Hummel T (2013) Characteristics of taste disorders. Eur Arch Otorhinolaryngol 270:1855-1860.

Femiano F, Scully C (2002) Burning mouth syndrome (BMS): double blind controlled study of alpha-lipoic acid (thioctic acid) therapy. J Oral Pathol Med 31: 267-269.

Femiano F, Scully C, Gombos F (2002) Idiopathic dysgeusia; an open trial of alpha lipoic acid (ALA) therapy. Int J Oral Maxillofac Surg 31(6):625-628.

Fjaeldstad A, Niklassen AS, Fernandes HM (2018) Re-Test Reliability of Gustatory Testing and Introduction of the Sensitive Taste-Drop Test. Chem Senses 43:341-346.

Fokkens WJ, Lund VJ, Hopkins C et al. (2020) European Position Paper on Rhinosinusitis and Nasal Polyps 2020. rhinology 58: 1-464.

Fokkens WJ et al (2012) European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl Mar:1-298.

Formaker B K, Mott AE, Frank ME (1988) The effects of topical anesthesia on oral burning in burning mouth syndrome. Ann N Y Acad Sci 855: 776-780

Forster G, Damm M, Gudziol H et al (2004) Epidemiology, pathophysiologic classification, diagnosis, and therapy. 52(8): 679-84.

Frasnelli J, Landis BN, Heilmann S, Hauswald B, Huttenbrink KB, Lacroix JS, Leopold DA, Hummel T (2003) Clinical presentation of qualitative olfactory dysfunction. Eur Arch Otorhinolaryngol 11:11-13.

Frasnelli JA, Temmel AF, Quint C, Oberbauer R, Hummel T (2002) Olfactory function in chronic renal failure. Am J Rhinol 16:275-279.

Frye RE, Schwartz BS, Doty RL (1990) Dose-related effects of cigarette smoking on olfactory function. JAMA 263:1233-1236.

Fujii M, Fukazawa K, Takayasu S, Sakagami M (2002) Olfactory dysfunction in patients with head trauma. Auris Nasus Larynx 29(1):35-40.

Fujiyama R, Ishitobi S, Honda K, Okada Y, Oi K, Toda K (2010) Ice cube stimulation helps to improve dysgeusia. Odontology 98(1):82-84.

Furukawa M, Kamide M, Takaki M, Umeda R (1988) Significance of intravenous olfaction test using thiamine propyldisulfide (allylamine) in oflactometry. Auris Nasus Larynx (Tokyo) 16:v.

Gambardella R. (1993) A Comparison of the Efficacy of Azelastine Nasal Spray and Loratidine Tablets in the Treatment of Seasonal Allergic Rhinitis. The Journal of International Medical Research 21(5):268-275.

Ganzer U, Arnold W (1997) Guideline olfactory disorders (clinical algorithm). ENT Communications 47: 3

Gehanno P, Deschamps E, Garay E, Baehre M, Garay RP (2001) Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. ORL J Otorhinolaryngol Relat Spec 63(2):76-81.

Geissler K, Reimann H, Gudziol H, Bitter T, Guntinas-Lichius O (2014) Olfactory training for patients with olfactory loss after upper respiratory tract infections. Eur Arch Otorhinolaryngol 271(6):1557-1562.

Genter MB, Doty RL (2019) Toxic exposures and the senses of taste and smell. Handb Clin Neurol 164:389-408

Gevaert P, Calus L, Van Zele T et al (2013) Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 131(1):110-116.

Gevaert P, Omachi TA, Corren J, et al. (2020) Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol. Sep 2020;146(3):595-605.

Gevorgyan A, Segboer C, Gorissen R, van Drunen CM, Fokkens W (2015) Capsaicin for non-allergic rhinitis. Cochrane Database Syst Rev 7:CD010591.

Gobba F. (2003) Occupational exposure to chemicals and sensory organs: a neglected research field. Neurotoxicology 24: 675-91

Glöckner L (1980) Clinical taste tests with chemical stimuli. Dissertation, Med Fak Univ Halle

Glöckner S (2000) Comparative studies of the sense of taste with dissolved and solid irritants. Dissertation, Med Fak Univ Halle

Golding-Wood DG, Holmstrom M, Darby Y, Scadding GK, Lund VJ (1996) The treatment of hyposmia with intranasal steroids. J Laryngol Otol 110(2):132-135.

Gorsky M, Silverman S, Jr & Chinn H. (1991). Clinical characteristics and management outcome in the burning mouth syndrome. An open study of 130 patients. Oral Surg Oral Med Oral Pathol 72, 192-195.

Gosepath J, Schaefer D, Amedee RG, Mann WJ (2001) Individual monitoring of aspirin desensitization. Arch Otolaryngol Head Neck Surg 127(3):316-321.

Gosepath J, Schafer D, Mann WJ (2002) Aspirin sensitivity: long term follow-up after up to 3 years of adaptive desensitization using a maintenance dose of 100 mg of aspirin a day. Laryngorhinootologie 81(10):732-738.

Grant R, Miller S, Simpson D, Lamey PJ, Bone I (1989) The effect of chorda tympani section on ipsilateral and contralateral salivary secretion and taste in man. J Neurol Neurosurg Psychiatry 52:1058-1062.

Greenway FL, Ingram DK, Ravussin E et al (2011) Loss of taste responds to high-dose biotin treatment. J Am Coll Nutr 30(3):178-181.

Groneberg DA, Heppt W, Cryer A et al (2003) Toxic rhinitis-induced changes of human nasal mucosa innervation. Toxicol Pathol 31(3):326-331.

Grouven U, Bender R, Ziegler A, Lange S (2007) Comparison of measurement methods. Dtsch Med Wochenschr 132 Suppl 1:e69-e73.

Grushka M, Epstein JB (1997) Burning mouth syndrome. In: Seiden AM (Ed.) Taste and smell disorders, Thieme New York, 159-171.

Grushka M, Epstein JB, Gorsky M (2003) Burning mouth syndrome and other oral sensory disorders: A unifying hypothesis. Pain Res Manag 8:133-135.

Gudziol H, Gramowski KH (1987) Respiratory olfactometry-an objectifying method for quantitative assessment of hyposmia. Laryngol Rhinol Otol 66:570-572.

Gudziol H, Förster G (2002) On the performance of preoperative olfactory tests from a medicolegal point of view.
Laryngorhinootologie 81:586-590.

Gudziol V, Lötsch J, Hähner A, Zahnert T, Hummel T (2006) Clinical significance of results from olfactory testing. Laryngoscope 116:1858-1863.

Gudziol H, Hummel T (2007) Normative values for the assessment of gustatory function using liquid tastants. Act Otolaryngol 127: 658-661

Gudziol H, Rahneberg K, Burkert S (2007) Anosmics taste worse than healthy individuals. Laryngorhinootologie 86:640-643.

Gudziol V, Hummel C, Negoias S, Ishimaru T, Hummel T (2007a) Lateralized differences in olfactory function. Laryngoscope 117(5):808-811.

Guilemany JM, Garcia-Pinero A, Alobid I et al. (2012) The loss of smell in persistent allergic rhinitis is improved by levocetirizine due to reduction of nasal inflammation but not nasal congestion (the CIRANO study). Int Arch Allergy Immunol 158(2):184-190.

Guinand N, Just T, Stow NW, Van HC, Landis BN (2010) Cutting the chorda tympani: not just a matter of taste. J Laryngol Otol 124:999-1002.

Gupta S, Lee JJ, Perrin A, Khan A, Smith HJ, Farrell N, Kallogjeri D, Piccirillo JF (2022) Efficacy and Safety of Saline Nasal Irrigation Plus Theophylline for Treatment of COVID-19-Related Olfactory Dysfunction: the SCENT2 Phase 2 Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg 148(12): 1132-1138.

Haberland EJ, Fikentscher R, Roseburg B (1974) A new electrogustometer. Mschr Otorhinolaryngology 108: 254-258

Haberland EJ, Seeber H, Gudziol H (1999) The sense of taste. mta 14: 5.

Haehner A, Boesveldt S, Berendse HW, Mackay-Sim A, Fleischmann J, Silburn PA, Johnston AN, Mellick GD, Herting B, Reichmann H, Hummel T (2009) Prevalence of smell loss in Parkinson's disease--a multicenter study. Parkinsonism Relat Disord 15:490-494.

Haehner A, Masala C, Walter S, Reichmann H, Hummel T (2019) Incidence of Parkinson's disease in a large patient cohort with idiopathic smell and taste loss. J Neurol 266: 339-345.

Hähner A, Mayer AM, Landis BN, Pournaras I, Lill K, Gudziol V, Hummel T (2009) High test-retest reliability of the extended version of the "Sniffin' Sticks" test. Chem Senses 34:705-711.

Hähner A, Tosch C, Wolz M et al. (2013) Olfactory training in patients with Parkinson's disease. PLoS One 8(4):e61680.

Hamada N, Endo S & Tomita H. (2002). Characteristics of 2278 patients visiting the Nihon University Hospital Taste Clinic over a 10-year period with special reference to age and sex distributions. Acta Otolaryngol Suppl, 7-15.

Hansen FS, Djupesland PG, Fokkens WJ (2010) Preliminary efficacy of fluticasone delivered by a novel device in recalcitrant chronic rhinosinusitis. Rhinology 48(3):292-299.

Hartog B, van Benthem PP, Prins LC, Hordijk GJ (1997) Efficacy of sinus irrigation versus sinus irrigation followed by functional endoscopic sinus surgery. Ann Otol Rhinol Laryngol 106(9):759-766.

Havel M, Ertl L, Braunschweig F et al. (2013) Sinonasal outcome under aspirin desensitization following functional endoscopic sinus surgery in patients with aspirin triad. Eur Arch Otorhinolaryngol 270(2):571-578.

Haxel BR, Bertz-Duffy S, Faldum A, Trellakis S, Stein B, Renner B, Kobal G, Letzel S, Mann WJ, Muttray A (2011) The candy smell test in clinical routine. Am J Rhinol Allergy 25: e145-8

Haxel BR, Nisius A, Fruth K, Mann WJ, Muttray A (2012) Deficits of medical consultation in olfactory disorders ENT 60(5) 432-438.

Heckmann JG, Heckmann SM, Lang CJ, Hummel T (2003) Neurological aspects of taste disorders. Arch Neurol 60: 667-671

Heckmann SM, Heckmann JG, Ungethüm A, Hujoel P, Hummel T (2006) Gabapentin has little or no effect in the treatment of Burning Mouth Syndrome: results of an open label pilot study. Eur J Neurol 13: e6-e7.

Heckmann SM, Hujoel P, Habiger S, Friess W, Wichmann M, Heckmann JG, Hummel T (2005) Zinc gluconate in the treatment of dysgeusia--a randomized clinical trial. J Dent Res 84:35-38.

Heckmann JG, Stossel C, Lang CJ, Neundorfer B, Tomandl B & Hummel T (2005) Taste disorders in acute stroke: a prospective observational study on taste disorders in 102 stroke patients. Stroke 36, 1690-1694.

Heilmann S, Hummel T (2004) A new method for comparing orthonasal and retronasal olfaction. Behav Neurosci 118:412-419.

Heilmann S, Hüttenbrink KB, Hummel T (2004) Local and systemic administration of corticosteroids in the treatment of olfactory loss. American Journal of Rhinology 18(1):29-33.

Heilmann S, Strehle G, Rosenheim K, Damm M, Hummel T (2002) Clinical assessment of retronasal olfactory function. Arch Otorhinolaryngol Head Neck Surg 128:414-418.

Heiser C, Landis BN, Giger R, Cao Van H, Guinand N, Hormann K & Stuck BA. (2010). Taste disturbance following tonsillectomy-a prospective study. Laryngoscope 120, 2119-2124.

Heiser C, Landis BN, Giger R, Cao Van H, Guinand N, Hormann K & Stuck BA. (2012). Taste disorders after tonsillectomy: A long-term follow-up. Laryngoscope 122, 1265-1266.

Helman SN, Adler J, Jafari A, Bennett S, Vuncannon JR, Cozart AC, Wise SK, Kuruvilla ME, Levy JM (2022) Treatment strategies for postviral olfactory dysfunction: a systematic review. Allergy Asthma Proc 43: 96-105.

Helms JA, Della-Fera MA, Mott AE, Frank ME (1995) Effects of chlorhexidine on human taste perception. Arch Oral Biol 40: 913-920.

Hendriks APJ (1988) Olfactory dysfunction. Rhinology 26:229-251.

Henkin RI (1986) Drug effects on smell and taste. In: Pharmacology in medicine: principles and practice(Pradham, S. N. et al., eds), pp 748-753 Bethesda: SP Press Int.

Henkin RI (1994) Drug-induced taste and smell disorders. Drug Safety 11: 318-377

Henkin RI, Gill JR, Bartter FC (1963) Studies on taste thresholds in normal man and in patients with adrenal cortical insufficiency: the role of acrenal cortical steroids and serum sodium concentration. J Clin Invest 42: 727-735

Henkin RI, Larson AL, Powell RD (1975) Hypogeusia, dysgeusia, hyposmia, and dysosmia Following Influenza-Like Infection. Annals of Otology Rhinology and Laryngology 84(5):672-682.

Henkin RI, Levy LM, Lin CS (2000) Taste and smell phantoms revealed by brain functional MRI (fMRI). J Comput Assist Tomogr 24(1):106-123.

Henkin RI, Potolicchio SJ, Jr, Levy LM (2011) Improvement in smell and taste dysfunction after repetitive transcranial magnetic stimulation. Am J Otolaryngol 32(1):38-46.

Henkin RI, Schecter PJ, Friedewald WT, Demets DL, Raff M (1976) A double blind study of the effects of zinc sulfate on taste and smell dysfunction. Am J Med Sci 272(3):285-299.

Henkin RI, Schultz M, Minnick-Poppe L (2012a) Intranasal theophylline treatment of hyposmia and hypogeusia: a pilot study. Arch Otolaryngol Head Neck Surg 138(11):1064-1070.

Henkin RI, Velicu I, Schmidt L (2009) An open-label controlled trial of theophylline for treatment of patients with hyposmia. Am J Med Sci 337(6):396-406.

Hernandez AK, Woosch D, Haehner A, Hummel, T (2022) Omega-3 supplementation in postviral olfactory dysfunction: a pilot study. Rhinology, 60: 139-144.

Hessler JL, Piccirillo JF, Fang D et al (2007) Clinical outcomes of chronic rhinosinusitis in response to medical therapy: results of a prospective study. Am J Rhinol 21(1):10-18.

Higaki T, Okano M, Makihara S et al (2012) Early interventional treatment with intranasal corticosteroids compared with postonset treatment in pollinosis. Ann Allergy Asthma Immunol 109(6):458-464.

Hintschich CA, Dietz M, Haehner A, Hummel T (2022) Topical Administration of Mometasone Is Not Helpful in Post-COVID-19 Olfactory Dysfunction. Life (Basel) 12: 1483.

Hissaria P, Smith W, Wormald PJ et al (2006) Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. J Allergy Clin Immunol 118(1):128-133.

Hoffman HJ, Ishii EK, MacTurk EH (1988) Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS). Ann N Y Acad Sci 855: 716-722.

Holbrook E, Leopold D, Schwob J (2005) Abnormalities of axon growth in human olfactory mucosa. Laryngoscope 115:2144-2154.

Holmstrom M (1999) Clinical performance of fluticasone propionate nasal drops. Allergy 54 Suppl 53:21-25.

Hong SC, Holbrook EH, Leopold DA, Hummel T (2012) Distorted olfactory perception: a systematic review. Acta Otolaryngol 132 Suppl 1: S27-31.

Hotta M, Endo S & Tomita H. (2002). Taste disturbance in two patients after dental anesthesia by inferior alveolar nerve block. Acta Otolaryngol Suppl, 94-98.

Hüttenbrink KB, Hummel T, Berg D, Gasser T, Hähner A. Olfactory dysfunction: common in old age and important early symptom of neurodegenerative diseases. Dtsch Arztebl Int 2013; 110(1-2):1-7, e1.

Hummel C, Frasnelli J, Gerber J et al (2007) Cerebral processing of gustatory stimuli in patients with taste loss. Behav Brain Res 185: 59-64

Hummel T (2000) Perspectives in Olfactory Loss Following Viral Infections of the Upper Respiratory Tract Arch Otolaryngol Head Neck Surg 126(6):802-803.

Hummel T, Erras A, Kobal G (1997) A new test for the screening of taste function. Rhinology 35: 146-148

Hummel T, Heilmann S, Hüttenbrink KB (2002) Lipoic acid in the treatment of smell dysfunction following viral infection of the upper respiratory tract. Laryngoscope 112(11):2076-2080.

Hummel T, Heilmann S, Landis BN, Frasnelli J, Small DM, Gerber J (2006) Perceptual differences between chemical stimuli presented through the ortho- or retronasal route. Flav Fragr J 21:42-47.

Hummel T, Genow A, Landis BN (2010) Clinical assessment of human gustatory function using event-related potentials. J Neurol Neurosurg Psychiatry 81: 459-464.

Hummel T, Klimek L, Welge-Lüssen A, Wolfensberger G, Gudziol H, Renner B, Kobal G (2000) Chemosensory evoked potentials for clinical diagnosis of olfactory disorders. HNO 48:481- 485.

Hummel T, Kobal G, Gudziol H, Mackay-Sim A (2007) Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol 264:237-243.

Hummel T, Konnerth CG, Rosenheim K, Kobal G (2001) Screening of olfactory function with a four-minute odor identification test: reliability, normative data, and investigations in patients with olfactory loss. Ann Otol Rhinol Laryngol 110:976-981.

Hummel T, Rissom K, Reden J, Haehner A, Weidenbecher M, Huettenbrink KB. Effects of olfactory training in patients with olfactory loss. Am J Rhinol. 2009;119:496-499.

Hummel T, Rothbauer C, Barz S, Grosser K, Pauli E, Kobal G (1998) Olfactory function in acute rhinitis. Olfaction and Taste Xii 855:616-624.

Hummel T, Scheibe M, Zahnert T, Landis BN (2007) Impact of nonallergic rhinitis on chemosensory function. Clin Allergy Immunol 19:389-400.

Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G (1997) 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 22(1):39-52.

Hummel T, Welge-Luessen A. Olfactory and gustatory disorders- physiology, pathophysiology and therapeutic approaches. Stuttgart, New York: Thieme Verlag, 2009b.

Hummel, T, Whitcroft KL, Rueter G, Haehner A (2017) Intranasal vitamin A is beneficial in post-infectious olfactory loss. Eur Arch Otorhinolaryngol, 274: 2819-2825.

Hummel T et al. (2017) Position paper on olfactory dysfunction. Rhinology Suppl. 25: 1-30.

Hunter SR, Hannum ME, Pellegrino R, O'Leary MA, Rawson NE, Reed DR, Dalton PH, Parma V (2023) Proof-of-concept: SCENTinel 1.1 rapidly discriminates COVID-19-related olfactory disorders. Chem Senses 48: bjad002.

Hura N, Xie DX, Choby GW, Schlosser RJ, Orlov CP, Seal SM, Rowan NR (2020) Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations. Int Forum Allergy Rhinol 10: 1065-1086.

Iannilli E, Noennig N, Hummel T, Schoenfeld AM (2014) Spatio-temporal correlates of taste processing in the human primary gustatory cortex. Neuroscience 273: 92-99

Ikeda K, Sakurada T, Takasaka T, Okitsu T, Yoshida S (1995) Anosmia following head trauma: preliminary study of steroid treatment. Tohoku J Exp Med 177(4):343-351.

Ikui A (2022) A review of objective measures of gustatory function. Acta Otolaryngol Suppl 546: 60-

68. Isenmann S, Haehner A, Hummel T (2021) Disorders of chemosensory function in covid-19: Pathomechanisms and clinical relevance. Fortschr Neurol Psychiatr 89: 281-288.

Jadad AR, Moore RA, Carroll D et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17(1):1-12.

Jafek BW, Johnson EW, Eller P, Murrow B. Olfactory mucosal biopsy and related histology. Taste and Smell Disorders. Thieme, NY, 1997.

Jafek BW, Murrow B, Michaels R, Restrepo D, Linschoten M (2002) Biopsies of human olfactory epithelium. Chemical Senses 27(7):623-628.

Jankowski R, Bodino C (2003) Olfaction in patients with nasal polyposis: effects of systemic steroids and radical ethmoidectomy with middle turbinate resection (nasalization). Rhinology 41(4):220-230.

Jankowski R, Klossek JM, Attali V, Coste A, Serrano E (2009) Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of nasal polyposis. Allergy 64(6):944-950.

Jiang RS, Lu FJ, Liang KL et al (2008) Olfactory function in patients with chronic rhinosinusitis before and after functional endoscopic sinus surgery. Am J Rhinol 22(4):445-448.

Jiang RS, Twu CW, Liang KL (2015) Medical treatment of traumatic anosmia. Otolaryngol Head Neck Surg 152(5):954-958.

Jiang RS, Wu SH, Liang KL, Shiao JY, Hsin CH, Su MC (2010) Steroid treatment of posttraumatic anosmia. Eur Arch Otorhinolaryngol 267(10):1563-1567.

Jiang RS, Twu CW, Liang KL (2019) The effect of olfactory training on odor identification in patients with traumatic anosmia. Int Forum Allergy Rhinol, 9, 1244-1251.

Just T, Pau HW, Bombor I, Guthoff RF, Fietkau R, Hummel T (2005) Confocal microscopy of the peripheral gustatory system: comparison between healthy subjects and patients suffering from taste disorders during radiochemotherapy. Laryngoscope 115:2178-2182.

Just T, Pau HW, Witt M, Hummel T (2006) Contact endoscopic comparison of morphology of human fungiform papillae of healthy subjects and patients with transected chorda tympani nerve. Laryngoscope 116:1216-1222.

Kadohisa M (2013) Effects of odor on emotion, with implications. Front Syst Neurosci 7:66.

Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ (2012) Topical steroids for nasal polyps. Cochrane Database Syst Rev 12:CD006549.

Kalish L, Snidvongs K, Sivasubramaniam R, Cope D, Harvey RJ (2016) WITHDRAWN: Topical steroids for nasal polyps. Cochrane Database Syst Rev 4:CD006549.

Kalish LH, Arendts G, Sacks R, Craig JC (2009) Topical steroids in chronic rhinosinusitis without polyps: a systematic review and meta-analysis. Otolaryngol Head Neck Surg 141(6):674-683.

Kalpaklioglu AF, Kavut AB (2010) Comparison of azelastine versus triamcinolone nasal spray in allergic and nonallergic rhinitis. Am J Rhinol Allergy 24(1):29-33.

Karstensen HG, Tommerup N (2012) Isolated and syndromic forms of congenital anosmia. Clin Genet 81:210-215.

Keith P, Nieminen J, Hollingworth K, Dolovich J (2000) Efficacy and tolerability of fluticasone propionate nasal drops 400 microgram once daily compared with placebo for the treatment of bilateral polyposis in adults. Clin Exp Allergy 30(10):1460-1468.

Kettenmann B, Hummel T, Kobal G (2001) Functional imaging of olfactory activation in the human brain. In: Methods and frontiers in chemosensory research (Simon, S. A. and Nicolelis, M. A. L., eds), pp 477-506 Boca Raton, Florida, USA: CRC press.

Khan M et al (2021) Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. Cell 184: 5932-5949.e5915.

Kieff DA, Busaba NY (2005) Efficacy of montelukast in the treatment of nasal polyposis. Ann Otol Rhinol Laryngol 114(12):941-945.

Kim BY, Park JY, Kim EJ, Kim BG, Kim SW, Kim SW (2019) The neuroplastic effect of olfactory training to the recovery of olfactory system in mouse model. Int Forum Allergy Rhinol 9:715-723.

Kirtsreesakul V, Hararuk K, Leelapong J, Ruttanaphol S (2015) Clinical efficacy of nasal steroids on nonallergic rhinitis and the associated inflammatory cell phenotypes. Am J Rhinol Allergy 29(5):343-349.

Klasser GD, Grushka M, Su N (2016) Burning mouth syndrome. Oral Maxillofac Surg Clin North Am 28 :381-96.

Klimek L, Eggers G (1997a) Olfactory dysfunction in allergic rhinitis is related to nasal eosinophilic inflammation. J Allergy Clin Immunol 100(2):158-164.

Klimek L, Moll B, Amedee RG, Mann WJ (1997b) Olfactory function after microscopic endonasal surgery in patients with nasal polyps. Am J Rhinol 11(4):251-255.

Klimek et al. (2017) Olfaction in patients with allergic rhinitis: an indicator of successful MP-AzeFlu therapy. Int Forum Allergy Rhinol 7(3):287-292.

Knecht M, Hüttenbrink KB, Hummel T (1999) Disorders of olfaction and tasting. Schweiz Med Wochenschr 129:1039-1046.

Kobal G (1981) Electrophysiological studies of the human sense of smell. Stuttgart: Thieme Verlag.

Kobal G et al. (2000) Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur Arch Otorhinolaryngol 257:205-211.

Kobal GK, et al. (2000) Multicenter investigation of 1036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur Arch Otorhinolaryngol 257:205-211.

Kohler CG, Moberg PJ, Gur RE, O'Connor MJ, Sperling MR, Doty RL (2001). Olfactory dysfunction in schizophrenia and temporal lobe epilepsy. Neuropsychiatry Neuropsychol Behav Neurol 14(2):83-88.

Kondo H, Matsuda T, Hashiba M, Baba S (1998) A study of the relationship between the T&T olfactometer and the University of Pennsylvania Smell Identification Test in a Japanese population. Am J Rhinol 12:353-358.

Konstantinidis I, Hummel T, Damm M et al. (2006) Post-infectious olfactory disfunction exhibits a seasonal pattern. Rhinology 44:135-139.

Konstantinidis I, Tsakiropoulou E, Bekiaridou P, Kazantzidou C, Constantinidis J. Use of olfactory training in post-traumatic and postinfectious olfactory dysfunction. Laryngoscope 2013; 123(12):E85-E90.

Krause S (2000) Functional results after remedial ear surgery in patients with chronic bone conduction. Dissertation, Med Fak Univ Jena

Krismer F et al (2017) Sniffing the diagnosis: Olfactory testing in neurodegenerative parkinsonism. Parkinsonism Relat Disord:35:36-41.

Kroflic B, Coer A, Baudoin T, Kalogjera L (2006) Topical furosemide versus oral steroid in preoperative management of nasal polyposis. Eur Arch Otorhinolaryngol 263(8):767-771.

Ku JY, Lee MK, Choi WR, Lee JH, Kim JH (2022) Effect of olfactory bulb atrophy on the success of olfactory training. Eur Arch Otorhinolaryngol 279: 1383-1389.

Kumbargere Nagraj S, George RP, Shetty N, Levenson D, Ferraiolo DM, Shrestha A (2017) Interventions for managing taste disturbances. Cochrane Database Syst Rev, 12: Cd010470.

Kuo CL, Shu CH (2015) Risk of decline and chance of improvement in olfaction among patients with post-traumatic olfactory loss. J Laryngol Otol 129(12):1201-1207.

Kutlu A, Salihoglu M, Haholu A, Cesmeci E, Cincik H, Ozturk S (2013) Short-term Beneficial Effect of Aspirin in Patient with Chronic Rhinosinusitis and Tolerant to Acetylsalicylic Acid. Iran J Allergy Asthma Immunol 12(4):400-403.

Landis BN, Beutner D, Frasnelli J, Hüttenbrink KB, Hummel T (2005) Gustatory function in chronic inflammatory middle ear diseases. Laryngoscope 115(6):1124-1127.

Landis BN, Frasnelli J, Croy I, Hummel T (2010a) Evaluating the clinical usefulness of structured questions in parosmia assessment. Laryngoscope 120(8):1707-1713.

Landis BN, Frasnelli J, Reden J, Lacroix JS, Hummel T (2005b) Differences between orthonasal and retronasal olfactory functions in patients with loss of the sense of smell. Arch Otolaryngol Head Neck Surg 131:977-981.

Landis BN, Giger R, Ricchetti A, Leuchter I, Hugentobler M, Hummel T, Lacroix JS (2003) Retronasal olfactory function in nasal polyposis. Laryngoscope 113:1993-1997.

Landis BN, Giger R, Dulguerov P, Hugentobler M, Hummel T & Lacroix JS. (2007). Gustatory function after microlaryngoscopy. Acta Otolaryngol 127, 1086-1090.

Landis BN & Guinand NO (2009). Selective taste disorder after temporal bone fracture. J Clin Neurosci 16, 605.

Landis BN, Hummel T, Lacroix JS (2005) Basic and clinical aspects of olfaction. Adv Tech Stand Neurosurg 30:69-105.

Landis BN, Just T (2009) Tasting disorders. In: Olfactory and gustatory disorders (Hummel, T. and Welge- Luessen, A., eds), pp 95-106 Stuttgart: Georg Thieme Verlag KG.

Landis BN, Just T (2010) Tasting disorders. ENT 58:650-655

Landis BN, Konnerth CG, Hummel T (2004) A study on the frequency of olfactory dysfunction. Laryngoscope 114:1764-1769.

Landis BN, Leuchter I, San Millan Ruiz D, Lacroix JS & Landis T. (2006). Transient hemiageusia in cerebrovascular lateral pontine lesions. J Neurol Neurosurg Psychiatry 77, 680-683.

Landis BN, Lacroix JS (2006) Postoperative/posttraumatic gustatory dysfunction. Adv Otorhinolaryngol 63:242-254.

Landis BN, Stow NW, Lacroix JS, Hugentobler M, Hummel T (2009) Olfactory disorders: the patients' view. Rhinology 47: 454-459.

Landis BN, Reden J, Haehner A (2010b) Idiopathic phantosmia: outcome and clinical significance. ORL J Otorhinolaryngol Relat Spec 72(5):252-255.

Landis BN, Scheibe M, Weber C et al. (2010c) Chemosensory interaction: acquired olfactory impairment is associated with decreased taste function. J Neurol 257(8):1303-1308.

Landis BN, Welge-Luessen A, Brämerson A, Bende M, Mueller CA, Nordin S, Hummel T (2009) "Taste Strips" - a rapid, lateralized, gustatory bedside identification test based on impregnated filter papers. J Neurol 256:242-248.

Lang NP, Catalanotto FA, Knopfli RU, Antczak AA (1988) Quality-specific taste impairment following the application of chlorhexidine digluconate mouthrinses. J Clin Periodontol 15: 43-48.

Langdon C et al. (2018) Olfactory Training in Post-Traumatic Smell Impairment: Mild Improvement in Threshold Performances: Results from a Randomized Controlled Trial. J Neurotrauma, 35: 2641-2652.

Langdon et al. (2016) Allergic rhinitis causes loss of smell in children: The OLFAPEDRIAL study. Pediatr Allergy Immunol 27(8):867-870.

Lapid H, Hummel T (2013) Recording odor-evoked response potentials at the human olfactory epithelium. Chem Senses 38:3-17.

Le Floch JP et al (1989) Taste impairment and related factors in type I diabetes mellitus. Diabetes Care 12: 173-178

Lee JY, Simon RA, Stevenson DD (2007) Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol 119(1):157-164.

Leon-Sarmiento FE, Leon-Ariza DS, Doty RL (2013) Dysfunctional chemosensation in myasthenia gravis: a systematic review. J Clin Neuromuscul Dis 15:1-6.

Lildholdt T, Rundcrantz H, Bende M, Larsen K (1997) Glucocorticoid treatment for nasal polyps. The use of topical budesonide powder, intramuscular betamethasone, and surgical treatment. Arch Otolaryngol Head Neck Surg 123(6):595-600.

Lildholdt T, Rundcrantz H, Lindqvist N (1995) Efficacy of Topical Corticosteroid Powder for Nasal Polyps. - A Double-Blind, Placebo-Controlled Study of Budesonide. Clinical Otolaryngology 20(1):26-30.

Liu DT, Sabha M, Damm M, Philpott C, Oleszkiewicz A, Hähner A, Hummel T (2021) Parosmia is Associated with Relevant Olfactory Recovery After Olfactory Training. Laryngoscope 131: 618-623.

Liu DT, Welge-Lüssen A, Besser G, Mueller CA, Renner B (2020) Assessment of odor hedonic perception: the Sniffin' sticks parosmia test (SSParoT). Sci Rep 10: 18019.

Livermore A, Laing DG (1996) Influence of training and experience on the perception of multicomponent odor mixtures. Journal of Experimental Psychology-Human Perception and Performance 22(2):267-277.

London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. (2008) Predictors of prognosis in patients with olfactory disturbance. Ann Neurol. 63(2):159-66.

Long A, McFadden C, DeVine D, Chew P, Kupelnick B, Lau J (2002) Management of allergic and nonallergic rhinitis. Evid Rep Technol Assess (Summ)(54):1-6.

Lötsch J, Reither N, Bogdanov V, Hähner A, Ultsch A, Hill K, Hummel T (2015) A brain-lesion pattern based algorithm for the diagnosis of post-traumatic olfactory loss. Rhinology 53:365-370.

Lötsch J, Ultsch A, Eckhardt M, Huart C, Rombaux P, Hummel T (2016) Brain lesion-pattern analysis in patients with olfactory dysfunctions following head trauma. Neuroimage Clin 11:99-105.

Lucassen EB, Turel A, Knehans A, Huang X, Eslinger P (2016) Olfactory dysfunction in multiple sclerosis: A scoping review of the literature. Mult Scler Relat Disord 6:1-9.

Lund VJ, Black JH, Szabo LZ, Schrewelius C, Akerlund A (2004) Efficacy and tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients. Rhinology 42(2):57-62.

Mahajan SK, Abbasi AA, Prasad AS, Rabbani P, Briggs WA, McDonald FD (1982) Effect of oral zinc therapy on gonadal function in hemodialysis patients. A double-blind study. Ann Intern Med 97(3):357-361.

Mahajan SK, Prasad AS, Lambujon J, Abbasi AA, Briggs WA, McDonald FD (1980) Improvement of uremic hypogeusia by zinc: a double blind study. Am J Clin Nutr 33: 1517-1521.

Mainland JD et al (2020) Identifying treatments for taste and smell disorders: gaps and opportunities. Chem Senses, 45: 493-502.

Manzi B1, Hummel T (2014) Intensity of regionally applied tastes in relation to administration method: an investigation based on the "taste strips" test. Eur Arch Otorhinolaryngol. 2014 Feb;271(2):411- 415

Martinez-Devesa P, Patiar S (2011) Oral steroids for nasal polyps. Cochrane Database Syst Rev(7):CD005232.

Mattes RD, Pawlik MK (2004) Effects of Ginkgo biloba on alertness and chemosensory function in healthy adults. Hum Psychopharmacol 19(2):81-90.

Meltzer EO, Jalowayski AA, Orgel HA, Harris AG (1998) Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. J Allergy Clin Immunol 102(1):39-49.

Merkonidis C, Gudziol V, Cecchini MP et al (2012) Improvement of chronic rhinitis under aspirin. Respir Care 57(3):460-463.

Merkonidis C, Grosse F, Ninh T, Hummel C, Haehner A, Hummel T (2015) Characteristics of chemosensory disorders--results from a survey. Eur Arch Otorhinolaryngol 272(6):1403-16. doi: 10.1007/s00405-014-3210-4. epub 2014 Aug 3.

Mesholam RI, Moberg PJ, Mahr RN, Doty RL (1998) Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Arch Neurol 55:84-90.

Mirza N, Machtay M, Devine PA, Troxel A, Abboud SK & Doty RL. (2008). Gustatory impairment in patients undergoing head and neck irradiation. Laryngoscope 118, 24-31.

Mortazavi H, Shafiei S, Sadr S, Safiaghdam H (2018) Drug-related dysgeusia: A Systematic Review. Oral Health Prev Dent 16: 499-507.

Moscovich M, Munhoz RP, Teive HA, Raskin S, Carvalho Mde J, Barbosa ER, Ranvaud R, Liu J, McFarland K, Ashizawa T, Lees AJ, Silveira-Moriyama L (2012) Olfactory impairment in familial ataxias. J Neurol Neurosurg Psychiatry 83:970-974.

Moberg PJ et al. (2014) Meta-analysis of olfactory function in schizophrenia, first-degree family members, and youths at-risk for psychosis. Schizophr Bull 40(1):50-59.

Mostafa BE, Abdel HH, Mohammed HE, Yamani M (2005) Role of leukotriene inhibitors in the postoperative management of nasal polyps. ORL J Otorhinolaryngol Relat Spec 67(3):148-153.

Mozell MM (1964) Evidence for sorption as a mechanism of the olfactory analysis of vapours. Nature 203:1181-1182.

Mueller CA, Khatib S, Landis BN, Temmel AFP, Hummel T (2007) Gustatory function after tonsillectomy. Arch Otolaryngol Head Neck Surg 133: 668-671

Mueller CA, Kallert S, Renner B, Stiassny K, Temmel AF, Hummel T, Kobal G (2003) Quantitative assessment of gustatory function in a clinical context using impregnated "taste strips". Rhinology 41: 2-6

Mueller CA, Pintscher K, Renner B (2011) Clinical test of gustatory function including umami taste. Ann Otol Rhinol Laryngol, 120: 358-362.

Mueller CA, Grassinger E, Naka A, Temmel AF, Hummel T, Kobal G (2006) A self-administered odor identification test procedure using the "Sniffin' Sticks". Chem Senses 31:595-598.

Müller CA, Reiter M, Renner B (2007) Diagnosis of olfactory and gustatory disorders in routine clinical practice. Laryngo-Rhino-Otologie 86:630-633.

Mullol J et al (2022) Olfactory Outcomes With Dupilumab in Chronic Rhinosinusitis With Nasal Polyps. J Allergy Clin Immunol Pract 10: 1086-1095. e5.

Murphy C, Gilmore MM, Seery CS, Salmon DP, Lasker BR (1990) Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. Neurobiol Aging 11(4):465-469.

Murphy C, Quinonez C, Nordin S (1995) Reliability and validity of electrogustometry and its application to young and elderly persons. Chem Senses 10:499-503.

Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM (2002) Prevalence of olfactory impairment in older adults. Jama 288:2307-2312.

Muttray A, Haxel B, Mann W, Letzel S (2006) Anosmia and rhinitis due to occupational solvent exposure. HNO 54(11):883-887.

Naka A, Riedl M, Luger A, Hummel T, Mueller CA (2010) Clinical significance of smell and taste disorders in patients with diabetes mellitus. Eur Arch Otorhinolaryngol 267:547-550.

Nakanishi, M et al. (2022) The digital scent device as a new concept for olfactory assessment. Int Forum Allergy Rhinol.

Nakazato Y, Ito Y, Naito S, Tamura N & Shimazu K. (2008). Dysgeusia limited to sweet taste in myasthenia gravis. Intern Med 47, 877-878.

Negoias S et al. (2010) Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression. Neuroscience 169(1):415-421.

Neta FI, Fernandes ACL, Vale AJM, Pinheiro FI, Cobucci RN, Azevedo EP, Guzen FP (2021) Pathophysiology and possible treatments for olfactory-gustatory disorders in patients affected by COVID-19. Curr Res Pharmacol Drug Discov 2: 100035.

Nin T, Sakagami M, Sone-Okunaka M, Muto T, Mishiro Y & Fukazawa K. (2006). Taste function after section of chorda tympani nerve in middle ear surgery. Auris Nasus Larynx 33, 13-17.

Nishimoto K, Horita R, Egawa M, Furuta S (1996) Clinical evaluation of taste dysfunction using a salt-impregnated taste strip. ORL 58:258-261.

Nordin S, Paulsen JS, Murphy C (1995) Sensory- and memory-mediated olfactory dysfunction in Huntington's disease. J Int Neuropsychol Soc 1:281-290.

Nuessle TM, Garneau NL, Sloan MM, Santorico SA (2015) Denver Papillae Protocol for Objective Analysis of Fungiform Papillae. J Vis Exp 100: e52860.

Ohla K et al (2022) A follow-up on quantitative and qualitative olfactory dysfunction and other symptoms in patients recovering from COVID-19 odor loss. Rhinology doi: 10.4193/rhin21.415

Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T (2019). Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol 276: 719-728.

Onoda K, Ikeda M, Sekine H & Ogawa H. (2012). Clinical study of central taste disorders and discussion of the central gustatory pathway. J Neurol 259, 261-266.

Orlandi RR, Kingdom TT, Hwang PH et al (2016) International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. Int Forum Allergy Rhinol 6 Suppl 1: S22-209.

Pade J, Hummel T (2008) Olfactory function following nasal surgery. Laryngoscope 118(7):1260-1264.

Panagiotopoulos G, Naxakis S, Papavasiliou A, Filipakis K, Papatheodorou G., Goumas P (2005). Decreasing nasal mucus Ca++ improves hyposmia. Rhinology 43: 130-134.

Panel on Communicative Disorders to the National Advisory Neurological and Communicative Disorders and Stroke Council (1979) NIH publication no. 79-1914. Washington, D.C.: Public Health Service.

Parma V, Hannum ME, O'Leary M, Pellegrino R, Rawson NE, Reed DR, Dalton PH (2021) SCENTinel 1.0: Development of a Rapid Test to Screen for Smell Loss. Chem Senses doi: 10.1093/chemse/bjab012.

Parnes SM, Chuma AV (2000) Acute effects of antileukotrienes on sinonasal polyposis and sinusitis. Ear Nose Throat J 79(1):18-5.

Pauli C, Fintelmann R, Klemens C et al (2007) Polyposis nasi--Improvement of quality of life by leukotriene receptor antagonists. Laryngorhinootologie 86(4):282-286.

Patel ZM et al. (2022) International consensus statement on allergy and rhinology: Olfaction. Int Forum Allergy Rhinol, 12, 327-680.

Pavlidis P, Gouveris H, Gorgulla H, Hast HJ, Maurer J (2015) Electrogustometry and contact endoscopy findings in patients with head and neck malignancies treated with chemotherapy, radiotherapy, or radiochemotherapy. Chem Senses 40:165-171.

Pavlidis P, Schittek GA, Saratziotis A, Ferfeli M, Kekes G, Gouveris H (2021) Electrogustometry: normative data for stimulus duration, tongue site and age decline. Clin Otolaryngol 46: 767-774.

Pellegrino R, Han P, Reither N, Hummel T (2019) Effectiveness of olfactory training on different severities of posttraumatic loss of smell. Laryngoscope, 129: 1737-1743.

Pellegrino R, Mainland JD, Kelly CE, Parker JK, Hummel T (2021) Prevalence and correlates of parosmia and phantosmia among smell disorders. Chem Senses doi: 10.1093/chemse/bjab046.

Penttila M, Poulsen P, Hollingworth K, Holmstrom M (2000) Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 microg once daily and twice daily in the treatment of bilateral nasal polyposis: a placebo-controlled randomized study in adult patients. Clin Exp Allergy 30(1):94-102.

Petzold GC, Einhaupl KM & Valdueza JM. (2003). Persistent bitter taste as an initial symptom of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 74, 687-688.

Pfaar O et al. (2014) Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (OGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int 23(8):282-319.

Pfaar O, Beule AG, Laudien M, Stuck BA (2023) Expanded guideline group 'Biologics in CRScNP'. Therapy of chronic rhinosinusitis with polyposis nasi (CRScNP) with monoclonal antibodies (biologics): S2k guideline of the German Society of Otolaryngology, Head and Neck Surgery (DGHNO-KHC) and the German Society of General Practice and Family Medicine (DEGAM) ENT 71:256-263.

Philpott CM, Erskine SE, Clark A, Leeper A, Salam M, Sharma R, Murty GE, Hummel T. (2017) A randomised controlled trial of sodium citrate spray for non-conductive olfactory disorders. Clin otolaryngol 42: 1295-1302.

Pierce J, Halpern BP (1996) Orthonasal and retronasal odorant identification based upon vapor phase input from common substances. Chem Senses 21:529-543.

Pingel J, Ostwald J, Pau HW, Hummel T, Just T (2010) Normative data for a solution-based taste test. Eur Arch Otorhinolaryngol 267:1911-1917.

Pinto, J. M., N. Mehta, M. DeTineo, J. Wang, F. M. Baroody, and R. M. Naclerio. 2010. "A Randomized, Double-Blind, Placebo-Controlled Trial of Anti-IgE for Chronic Rhinosinusitis." Rhinology 48 (3): 318-24. https://doi.org/10.4193/Rhino09.144.

Pinto JM, Kern DW, Wroblewski KE, Chen RC, Schumm LP, McClintock MK (2014) Sensory function: insights from Wave 2 of the National Social Life, Health, and Aging Project. J Gerontol B Psychol Sci Soc Sci 69, Suppl 2:S144-S153.

Phillips B, Ball C, Sackett D et al (2009) Evidence types modified from Oxford Center for EbM. http://www.cebm.net/index.aspx?o=1025 .

Philpott CM, Boardman J, Boak, D (2021) Patient Experiences of Postinfectious Olfactory Dysfunction. ORL J Otorhinolaryngol Relat Spec, 83, 299-303.

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30: 1591-1601.

Prem B, Liu DT, Besser G, Renner B, Mueller CA (2022) Retronasal olfactory testing in early diagnosed and suspected COVID-19 patients: a 7-week follow-up study. Eur Arch Otorhinolaryngol 279: 257-265.

Printza A, Boziki M, Valsamidis C, Bakirtzis C, Constantinidis J, Grigoriadis N, Triaridis S (2022) Smell as a Disease Marker in Multiple Sclerosis. J Clin Med 11: 5215.

Quint C, Temmel AF, Hummel T, Ehrenberger K (2002) The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. Acta Otolaryngol 122(8):877- 881.

Radcliffe MJ, Lampe FC, Brostoff J (1996) Allergen-specific low-dose immunotherapy in perennial allergic rhinitis: a double-blind placebo-controlled crossover study. J Investig Allergol Clin Immunol 6(4):242-247.

Ragab S, Parikh A, Darby YC, Scadding GK (2001) An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. Clin Exp Allergy 31(9):1385-1391.

Rawal S, Hoffman HJ, Bainbridge KE, Huedo-Medina TB, Duffy VB (2016) Prevalence and risk factors of self-reported smell and taste alterations: results from the 2011-2012 US National Health and Nutrition Examination Survey (NHANES). Chem Senses 41:69-76.

Reden J, Herting B, Lill K, Kern R, Hummel T (2011) Treatment of Postinfectious Olfactory Disorders With Minocycline: A Double-Blind, Placebo-Controlled Study. Laryngoscope 121(3):679-682.

Reden J, Lill K, Zahnert T, Haehner A, Hummel T (2012) Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial. Laryngoscope 122(9):1906-1909.

Reden J, Mueller A, Mueller C et al (2006a) Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. Arch Otolaryngol Head Neck Surg 132(3):265-269.

Reden J, Mueller A, Mueller C, Konstantinidis I, Frasnelli J, Landis BN, Hummel T (2006) Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. Arch Otolaryngol Head Neck Surg 132:265-269.

Renner B, Mueller CA, Dreier J, Faulhaber S, Rascher W, Kobal G (2009) The candy smell test: a new test for retronasal olfactory performance. Laryngoscope 119:487-495.

Renzi G et al (2002) Taste and olfactory disturbances after upper and middle thord facial fractures: a preliminary study. Ann Plast Surg 48: 355-358

Ribas ES, Duffau H (2012) Permanent anosmia and ageusia after resection of the left temporoinsular low-grade glioma: anatomofunctional considerations. J Neurosurg 116: 1007-1013

Richter H (2002) Comparative determination of total palatability in normal subjects using palatability tablets and drops. Dissertation, Med Fak Univ Jena

Olfactory disorders. Epidemiology, pathophysiologic classification, diagnosis, and therapy. HNO 52(8):679-684.

Rombaux P, Huart C, Deggouj N, Duprez T, Hummel T (2012) Prognostic value of olfactory bulb volume measurement for recovery in postinfectious and posttraumatic olfactory loss. Otolaryngol Head Neck Surg 147:1136-1141.

Rombaux P, Mouraux A, Bertrand B, Nicolas G, Duprez T, Hummel T (2006) Olfactory function and olfactory bulb volume in patients with postinfectious olfactory loss. Laryngoscope 116(3):436-439.

Roos DS, Klein M, Deeg DJH, Doty RL, Berendse HW (2022) Prevalence of prodromal symptoms of Parkinson's disease in the late middle-aged population. J Parkinsons Dis 12: 967-974.

Roseburg B, Fikentscher R (1984) Olfactory and gustatory disorders. In: HNO-Begutachtung, 2 Aufl, pp 75- 80 Leipzig: Georg Thieme.

Rozsasi A, Polzehl D, Deutschle T et al. (2008) Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. Allergy 63(9):1228-1234.

Sahm K (1999) On the tasting ability of patients with head and neck tumors undergoing irradiation. Dissertation, Med Fak Univ Jena

Sahu RN, Behari S, Agarwal VK, Giri PJ & Jain VK. (2008). Taste dysfunction in vestibular schwannomas. Neurol India 56, 42-46.

Sakagami M, Ikeda M, Tomita H et al. (2009) A zinc-containing compound, polaprezinc, is effective for patients with taste disorders: randomized, double-blind, placebo-controlled, multi-center study. Acta Otolaryngol 129(10):1115-1120.

Sakai F, Yoshida S, Endo S, Tomita H (2002) Double-blind, placebo-controlled trial of zinc picolinate for taste disorders. Acta Otolaryngol Suppl(546):129-133.

Sandow PL, Hejrat-Yazdi M, Heft MW (2006) taste loss and recovery following radiation therapy. J Dent Res 85: 608-611

Sasano T, Satoh-Kuriwada S, Shoji N, Sekine-Hayakawa Y, Kawai M, Uneyama H (2010) Application of umami taste stimulation to remedy hypogeusia based on reflex salivation. Biol Pharm Bull 33(11):1791-1795.

Schäper C, Noga O, Koch B et al. (2011) Anti-inflammatory properties of montelukast, a leukotriene receptor antagonist in patients with asthma and nasal polyposis. J Investig Allergol Clin Immunol 21(1):51-58.

Schmidt E (1988) Sensitivity differences for the four basic qualities of taste on the human tongue. Dissertation, Med Fak Univ Halle

Schofield PW, Moore TM, Gardner A (2014) Traumatic brain injury and olfaction: a systematic review. Front Neurol 5:5.

Schönherr A (2001) Investigation of the local total tasting ability in patients with unilateral chorda tympani destruction and normal subjects. Dissertation, Med Fak Univ Jena

Schriever VA, Gupta N, Pade J, Szewczynska M, Hummel T (2013) Olfactory function following nasal surgery: a 1-year follow-up. Eur Arch Otorhinolaryngol 270(1):107-111.

Schumm LP, McClintock M, Williams S, Leitsch S, Lundstrom J, Hummel T, Lindau ST (2009) Assessment of sensory function in the National Social Life, Health, and Aging Project. J Gerontol B Psychol Sci Soc Sci 64 Suppl 1:i76-85.

Scott AE (1989) Caution urged in treating 'steroid-dependent anosmia'. Arch Otolaryngol Head Neck Surg 115: 109-110.

Scott JW, Sherrill L, Jiang J, Zhao K (2014) Tuning to odor solubility and sorption pattern in olfactory epithelial responses. J Neurosci 34:2025-2036.

Seiden AM (2004) Postviral olfactory loss. Otolaryngologic Clinics of North America 37(6):1159.

Sekine R, Menzel S, Hähner A, Mori E, Hummel T (2022) Assessment of postviral qualitative olfactory dysfunction using the short SSParoT in patients with and without parosmia. Eur Arch Orl (in press)

Sekine R, Hahner A, Laudien M, Mori E, Hummel, T (2022) Ratings of trigeminal stimulation in patients with olfactory loss. Rhinology, 60: 313-315.

Seo BS, Lee HJ, Mo JH, Lee CH, Rhee CS, Kim JW (2009) Treatment of postviral olfactory loss with glucocorticoids, Ginkgo biloba, and mometasone nasal spray. Arch Otolaryngol Head Neck Surg 135(10):1000-1004.

Settipane RA (2011) Other causes of rhinitis: mixed rhinitis, rhinitis medicamentosa, hormonal rhinitis, rhinitis of the elderly, and gustatory rhinitis. Immunol Allergy Clin North Am 31(3):457-467.

Settipane RA, Kaliner MA (2013) Chapter 14: Nonallergic rhinitis. Am J Rhinol Allergy 27 Suppl 1:S48-S51.

Settipane RA, Lieberman P (2001) Update on nonallergic rhinitis. Ann Allergy Asthma Immunol 86(5):494-507.

Shin et al. (2021) Serum vitamin D level is associated with smell dysfunction independently of aeroallergen sensitization, nasal obstruction, and the presence of allergic rhinitis in children. Pediatr Allergy Immunol 32(1):116-123.

Shu CH, Hummel T, Lee PL, Chiu CH, Lin SH, Yuan BC (2009) The proportion of self-rated olfactory dysfunction does not change across the life span. Am J Rhinol Allergy 23:413-416.

Shu CH, Lee PL, Shiao AS, Chen KT, Lan MY (2012) Topical corticosteroids applied with a squirt system are more effective than a nasal spray for steroid-dependent olfactory impairment. Laryngoscope 122: 747-750.

Shusterman D (2007) Environmental nonallergic rhinitis. Clin Allergy Immunol 19:249-266.

Siegel JK, Yuan X, Wroblewski KE, McClintock MK, Pinto JM (2021) Sleep-Disordered Breathing Is Associated With Impaired Odor Identification in Older U.S. Adults. J Gerontol A Biol Sci Med Sci 76(3):528-533.

Simmen D, Briner HR (2006) Olfaction in rhinology--methods of assessing the sense of smell. Rhinology 44:98-101.

Simmen D, Briner HR, Hess K (1999) Screening test of the sense of smell with olfactory disks. Laryngorhinootologie 78:125-130.

Sivam A, Jeswani S, Reder L et al (2010) Olfactory cleft inflammation is present in seasonal allergic rhinitis and is reduced with intranasal steroids. Am J Rhinol Allergy 24(4):286-290.

Slavin RG (2003) Occupational rhinitis. Ann Allergy Asthma Immunol 90(5 Suppl 2):2-6.

Small CB, Hernandez J, Reyes A et al (2005) Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. J Allergy Clin Immunol 116(6):1275-1281.

Small CB, Stryszak P, Danzig M, Damiano A (2008) Onset of symptomatic effect of mometasone furoate nasal spray in the treatment of nasal polyposis. J Allergy Clin Immunol 121(4):928-932.

Small DM, Gerber JC, Mak YE, Hummel T (2005) Differential neural responses evoked by orthonasal versus retronasal odorant perception in humans. Neuron 47:593-605.

Smutzer G, Lam S, Hastings L, Desai H, Abarintos RA, Sobel M, Sayed N (2008) A test for measuring gustatory function. Laryngoscope 118:1411-1416.

Snidvongs K, Kalish L, Sacks R, Craig JC, Harvey RJ (2011) Topical steroid for chronic rhinosinusitis without polyps. Cochrane Database Syst Rev(8):CD009274.

Snidvongs K, Kalish L, Sacks R, Craig JC, Harvey RJ (2016) WITHDRAWN: Topical steroid for chronic rhinosinusitis without polyps. Cochrane Database Syst Rev 4:CD009274.

Snidvongs K, Kalish L, Sacks R, Sivasubramaniam R, Cope D, Harvey RJ (2013) Sinus surgery and delivery method influence the effectiveness of topical corticosteroids for chronic rhinosinusitis: systematic review and meta-analysis. Am J Rhinol Allergy 27(3):221-233.

Snitz K et al. (2022) An olfactory self-test effectively screens for COVID-19. Comm Med 2: 34.

Sorokowska A, Albrecht E, Haehner A, Hummel T (2015a) Extended version of the "Sniffin' Sticks". identification test: test-retest reliability and validity. J Neurosci Meth 243: 111-114.

Sorokowska A, Albrecht E, Hummel T (2015b) Reading first or smelling first? Effects of presentation order on odor identification. Atten Percept Psychophys 77:731-736.

Sorokowska A, Drechsler E, Karwowski M, Hummel T (2017) Effects of olfactory training: a meta-analysis. Rhinology 55: 17-26.

Steffens Y, Le Bon SD, Lechien J, Prunier L, Rodriguez, A, Saussez S, Horoi M (2022) Effectiveness and safety of PRP on persistent olfactory dysfunction related to COVID-19. Eur Arch Otorhinolaryngol 279: 5951-5953.

Steinbach S et al. (2009) Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. J Clin Oncol 27:1899-1905.

Stenner M, Vent J, Huttenbrink KB, Hummel T, Damm M (2008) Topical therapy in anosmia: relevance of steroid-responsiveness. Laryngoscope 118(9):1681-1686.

Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA (1996) Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. J Allergy Clin Immunol 98(4):751-758.

Stevenson DD, Pleskow WW, Simon RA et al (1984) Aspirin-sensitive rhinosinusitis asthma: a double-blind crossover study of treatment with aspirin. J Allergy Clin Immunol 73(4):500-507.

Stewart RA, Ram B, Hamilton G, Weiner J, Kane KJ (2008) Montelukast as an adjunct to oral and inhaled steroid therapy in chronic nasal polyposis. Otolaryngol Head Neck Surg 139(5):682-687.

Stillman, J. A., R. P. Morton, et al. (2000). "Automated electrogustometry: a new paradigm for the estimation of taste detection thresholds." Clin Otolaryngol Allied Sci 25(2): 120-5.

Stjarne P, Blomgren K, Caye-Thomasen P, Salo S, Soderstrom T (2006a) The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. Acta Otolaryngol 126(6):606-612.

Stjarne P, Mosges R, Jorissen M et al (2006b) A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. Archives of Otolaryngology -- Head & Neck Surgery.

Stoll AL, Oepen G (1994) Zinc salts for the treatment of olfactory and gustatory symptoms in psychiatric patients: a case series. J Clin Psychiatry 55:309-311.

Stricker BH et al (1996) Taste loss to terbinafine: a case-control study of potential risk factors. Br J Clin Pharmacol 42: 313-318

Strutz J, Mann W. Practice of otolaryngology, head and neck surgery. 2nd ed. Stuttgart: Thieme, 2009.

Stuck BA, Beule A, Damm M et al. (2014) Position paper "Chemosensory testing in the expert assessment of olfactory disorders". Laryngorhinootol 93(5):327-329.

Stuck BA, Blum A, Hagner AE, Hummel T, Klimek L, Hormann K (2003) Mometasone furoate nasal spray improves olfactory performance in seasonal allergic rhinitis. Allergy 58(11):1195.

Stuck BA, Hummel T (2015) Olfaction in allergic rhinitis: A systematic review. J Allergy Clin Immunol 136(6):1460-1470.

Stuck BA, Beule A, Jobst D, Klimek L, Laudien M, Lell M, Vogl TJ, Popert U (2018) Guideline. "Rhinosinusitis" - Long version. ENT 66: 38-74.

Stuck BA, Muttray A. Assessment of olfactory and gustatory disorders. In: Hummel T, Welge-Lüssen A, eds. olfactory and gustatory disorders. Stuttgart: Georg Thieme Verlag, 2008; 123-136, 157-158.

Su N, Ching V, Grushka M (2013) Taste Disorders: A Review. J Can Dent Assoc 79:d86.

Sumner D (1964) Post-traumatic anosmia. Brain 87:107-120.

Suzuki M, Saito K, Min WP et al (2007) Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope 117(2):272-277.

Sweet JM, Stevenson DD, Simon RA, Mathison DA (1990) Long-term effects of aspirin desensitization-. -treatment for aspirin-sensitive rhinosinusitis-asthma. J Allergy Clin Immunol 85(1 Pt 1):59-65.

Tan BKJ et al. (2022) Prognosis and persistence of smell and taste dysfunction in patients with covid-19: meta-analysis with parametric cure modeling of recovery curves. Bmj, 378: e069503.

Tanaka O, Mukaino Y (1999) The effect of auricular acupuncture on olfactory acuity. American Journal of Chinese Medicine 27(1):19-24.

Temmel AF, Pabinger S, Quint C, Munda P, Ferenci P, Hummel T (2005) Dysfunction of the liver affects the sense of smell. Wien Klin Wochenschr 117:26-30.

Tolbert LP (1998) Olfactory development in invertebrates. On the scent of central. Ann N Y Acad Sci 855:95-103.

Tomita H (1982) Methods in taste examination. In: Surjan L, Bodo G (eds). Proc. XIIth ORL World Congr., Budapest, Hungary, 1981, Excerpta Medica Amsterdam, Oxford, 627.

Tomita H, Ikeda M (2002) Clinical use of electrogustometry: strengths and limitations. Acta Oto- Laryngol Suppl 546: 27-38

Tomita H, Ikeda M, Okuda Y (1986) Basis and practice of clinical taste examinations. Auris Nasus Larynx (Tokyo) 13 (suppl. 1):S1-S15.

Tomofuji S, Sakagami M, Kushida K, Terada T, Mori H & Kakibuchi M. (2005). Taste disturbance after tonsillectomy and laryngomicrosurgery. Auris Nasus Larynx 32, 381-386.

Tos M, Svendstrup F, Arndal H et al (1998) Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. Am J Rhinol 12(3):183-189.

Trecca EMC, Cassano M, Longo F, Petrone P, Miani C, Hummel T, Gelardi M (2022) Results from psychophysical tests of smell and taste during the course of SARS-CoV-2 infection: a review. Acta Otorhinolaryngol Ital 42, S20-s35.

Tuncer U, Soylu L, Aydogan B, Karakus F, Akcali C (2003) The effectiveness of steroid treatment in nasal polyposis. Auris Nasus Larynx 30(3):263-268.

van den Berg JW, de Nier LM, Kaper NM et al. (2014) Limited evidence: higher efficacy of nasal saline irrigation over nasal saline spray in chronic rhinosinusitis--an update and reanalysis of the evidence base. Otolaryngol Head Neck Surg 150(1):16-21.

Van Gerven L et al. (2021) Low-dose capsaicin (0.01 mM) nasal spray is equally effective as the current standard treatment for idiopathic rhinitis: A randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 147: 397-400.e394.

van Rijswijk JB, Boeke EL, Keizer JM, Mulder PG, Blom HM, Fokkens WJ (2003) Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study. Allergy 58(8):754-761.

van Rijswijk JB, Gerth vW (2006) Capsaicin treatment of idiopathic rhinitis: the new panacea? Curr Allergy Asthma Rep 6(2):132-137.

Van Zele T, Gevaert P, Holtappels G et al. (2010) Oral steroids and doxycycline: Two diffrent approches to treat nasal polyps. Journal of Allergy & Clinical Immunology.

Vennemann MM, Hummel T, Berger K (2008) The association between smoking and smell and taste impairment in the general population. J Neurol 255:1121-1126.

Vent J, Bartels S, Haynatzki G, Gentry-Nielsen MJ, Leopold DA, Hallworth R (2003). The impact of ethanol and tobacco smoke on intranasal epithelium in the rat. Am J Rhinol. 17(4):241-7.

Vent J, Koenig J, Hellmich M, Huettenbrink KB, Damm M (2010a) Impact of recurrent head trauma on olfactory function in boxers: a matched pairs analysis. Brain Res 1320:1-6.

Vent J, Wang DW, Damm M (2010b) Effects of traditional Chinese acupuncture in post-viral olfactory dysfunction. Otolaryngol Head Neck Surg 142(4):505-509.

Videler WJ, Badia L, Harvey RJ et al (2011) Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. Allergy 66(11):1457-1468.

Vlckova I, Navratil P, Kana R, Pavlicek P, Chrbolka P, Djupesland PG (2009) Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device. Rhinology 47(4):419-426.

Voirol E, Daget N (1986) Comparative study of nasal and retronasal olfactory perception. Food Sci Technol 19:316-319.

Vuralkan E, Saka C, Akin I et al (2012) Comparison of montelukast and mometasone furoate in the prevention of recurrent nasal polyps. Ther Adv Respir Dis 6(1):5-10.

Walliczek U, Negoias S, Hähner A, Hummel T (2016) Assessment of chemosensory function using "Sniffin' Sticks", taste strips, taste sprays, and retronasal olfactory tests. Curr Pharmac Des 22: 2245-2252.

Walliczek-Dworschak U, Pellegrino R, Lee S, Hummel C, Hähner A, Hummel T (2016) Olfactory Performance Can Be Influenced by the Presentation Order, Background Noise, and Positive Concurrent Feedback. Chem Senses 41: 697-701.

Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A (2006) A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope 116(2):189-193.

Wang LW, Chen LX, Jacob T (2004) Evidence for peripheral plasticity in human odour response. Journal of Physiology-London 554(1):236-244.

Wardrop RW, Hailes J, Burger H, Reade PC (1989) Oral discomfort at menopause. Oral Surg 67:535-540.

Webb DR, Meltzer EO, Finn AF, Jr et al (2002) Intranasal fluticasone propionate is effective for perennial nonallergic rhinitis with or without eosinophilia. Ann Allergy Asthma Immunol 88(4):385- 390.

Weiffenbach JM (1987) Taste perception mechanisms. Front Oral Physiol. 6: 151-167

Welge-Lüssen A (2009) Ageing, neurodegeneration, and olfactory and gustatory loss. B-ENT 5: 129-132

Weir EM, Hannum ME, Reed DR, Joseph PV, Munger SD, Hayes JE, Gerkin RC (2022) The Adaptive Olfactory Measure of Threshold (ArOMa-T): a rapid test of olfactory function. Chem Senses doi: 10.1093/chemse/bjac036.

Weiss T, Soroka T, Gorodisky L, Shushan S, Snitz K, Weissgross R, Furman-Haran E, Dhollander T, Sobel N (2019) Human olfaction without Apparent Olfactory Bulbs. Neuron 104: 1023.

Welge-Lüssen A, Hummel T (2009) Practical approach to patients with olfactory disorders. In: Olfactory and Tasting Disorders (Hummel, T. and Welge-Luessen, A., eds), pp 3-10 Stuttgart: Georg Thieme Verlag.

Welge-Lüssen A, Hummel T. Practical approach to patients with olfactory disorders. In: Hummel T, Welge-Lüssen A, editors. Olfactory and gustatory disorders. Georg Thieme Verlag Stuttgart, 2009: 3- 10.

Welge-Lüssen A, Gudziol V, Wolfensberger M, Hummel T (2010) Olfactory testing in clinical settings - is there additional benefit from unilateral testing? Rhinology 48(2):156-159.

Welge-Lüssen A, Dorig P, Wolfensberger M, Krone F, Hummel T (2011) A study about the frequency of taste disorders. J Neurol 258:386-392.

Welge-Lüssen A, Hilgenfeld A, Meusel T, Hummel T (2012) Long-term follow-up of posttraumatic olfactory disorders. Rhinology 50(1):67-72.

Welge-Luessen A, Leopold DA, Miwa T (2013) Smell and Taste Disorders - Diagnostic and Clinical Work- Up. In: Management of Smell and Taste Disorders - A Practical Guide for Clinicians(Welge-Luessen, A. and Hummel, T., eds), pp 49-57 Stuttgart: Thieme.

Wentzel JL, Soler ZM, DeYoung K, Nguyen SA, Lohia S, Schlosser RJ (2013) Leukotriene antagonists in nasal polyposis: a meta-analysis and systematic review. Am J Rhinol Allergy 27(6):482-489.

Wenzel BM (1948) Techniques in olfactometry: a critical review of the last one hundred years. Psychol Bull 45:230-247.

Whitcroft KL, Merkonidis C, Cuevas M, Haehner A, Philpott C, Hummel T (2016) Intranasal sodium citrate solution improves olfaction in post-viral hyposmia. Rhinology 54: 368-374.

Whitcroft KL, Ezzat M, Cuevas M, Andrews P, Hummel T (2017) The effect of intranasal sodium citrate on olfaction in post-infectious loss: results from a prospective, placebo-controlled trial in 49 patients. Clin otolaryngol 42: 557-563.

Whitcroft KL, Gunder N, Cuevas M, Andrews P, Menzel S, Haehner A, Hummel T (2021) Intranasal sodium citrate in quantitative and qualitative olfactory dysfunction: results from a prospective, controlled trial of prolonged use in 60 patients. Eur Arch Otorhinolaryngol 278(8): 2891-2897.

Wilken MK, Satiroff BA (2012) Pilot study of "miracle fruit" to improve food palatability for patients receiving chemotherapy. Clin J Oncol Nurs 16(5):E173-E177.

Williams AR, Mowlazadeh B, Sisler L, Williams PD (2015) Self-reported assessment of symptpoms and self-care within a cohort of U.S. veterans during outpatient care for cancer. Clin J Oncol Nurs 19: 595-602.

Windfuhr JP, Sack F, Sesterhenn AM, Landis BN, Chen YS (2010) Post-tonsillectomy taste disorders. Eur Arch Otorhinolaryngol. 267(2):289-93. doi: 10.1007/s00405-009-1057-x. Epub 2009 Aug 23.

Wober W, Diez Crespo CD, Bahre M (1997) Evaluation of the drug monitoring program of azelastine hydrochloride nasal spray in the treatment of allergic rhinitis in children under 13 years of age. Drug Research 47(7):841-844.

Wolf A, Varga L, Wittibschlager L, Renner B, Mueller CA (2015). A self-administered test of taste function using "Taste Strips". Int Forum Allergy Rhinol Dec 3. doi: 10.1002/alr.21681. [Epub ahead of print].

Yamagishi M, Nakamura H., Fujiwara M. (1994) Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. Rhinology 32:113-118.

Yamagishi M, Nakano Y (1992) A Reevaluation of the Classification of Olfactory Epithelia in Patients with Olfactory Disorders. European Archives of Oto-Rhino-Laryngology 249(7):393-399.

Yan CH, Mundy DC, Patel ZM (2020) The use of platelet-rich plasma in treatment of olfactory dysfunction: A pilot study. Laryngoscope investigative otolaryngology, 5, 187-193.

Yan CH et al. (2020) Effect of Omega-3 Supplementation in Patients With Smell Dysfunction Following Endoscopic Sellar and Parasellar Tumor Resection: A Multicenter Prospective Randomized Controlled Trial. Neurosurg 87: E91-e98.

Zabernigg A, Gamper EM, Giesinger JM et al (2010) Taste alterations in cancer patients receiving chemotherapy: a neglected side effect? Oncologist 15: 913-920

Zang Y, Han P, Joshi A, Hummel T (2021) Individual variability of olfactory fMRI in normosmia and olfactory dysfunction. . Eur Arch ORL 278: 379-387.

Zazhytska M et al. (2022) Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. Cell 185: 1052-1064.e1012.

Zernecke R, Frank T, Haegler K, Albrecht J, Bruckmann H, Wiesmann M (2011) Correlation analyses of detection thresholds of four different odorants. Rhinology 49:331-336.

Zhao K, Scherer PW, Hajiloo SA, Dalton P (2004) Effect of anatomy on human nasal air flow and odorant transport patterns: implications for olfaction. Chem Senses 29(5):365-379.

Zhu Y, Hummel T (2022) Assessment of Taste Function. Handb Exp Pharmacol, 275, 295-319.

5 Miscellaneous

Version number: 5.0

5.1 Creation date

05/1996

5.2 Last Revision

01.05.2023

5.3 Next review planned

30.04.2028

5.4 Contact

Prof. Dr med T. Hummel (Dresden, thomas.hummel@tu-dresden.de), Prof. Dr med M. Damm (Cologne, Prof.Damm@hno-heilkunde-koeln.de)