Continuing Medical Education

# Olfactory Dysfunction: Etiology, Diagnosis, and Treatment

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## Summary

Background: Disorders of the sense of smell have received greater attention because of the frequency with which they occur as a symptom of SARS-CoV-2 infection. Olfactory dysfunction can lead to profound reduction in quality of life and may arise from many different causes.

Methods: A selective literature review was conducted with consideration of the current version of the guideline issued by the Association of the Scientific Medical Societies in Germany.

Results: The cornerstones of diagnosis are the relevant medical history and psychophysical testing of olfactory function using standardized validated tests. Modern treatment strategies are oriented on the cause of the dysfunction. While treatment of the underlying inflammation takes precedence in patients with sinunasal dysosmia, olfactory training is the primary treatment option for other forms of the disorder. The prognosis is determined not only by the cause of the olfactory dysfunction and the patient's age, but also by the olfactory performance as measured at the time of diagnosis.

Conclusion: Options for the treatment of olfactory dysfunction are available but limited, depending on the cause. It is therefore important to carry out a detailed diagnostic work-up and keep the patient informed of the expected course and prognosis.

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Despite the widely held assumption that the human sense of smell is relatively poor, humans are actually more sensitive than other mammals to a range of odors (1).

Olfaction is unique among the senses in that the olfactory cells regenerate continuously (e1, 2). Another special feature of the human sense of smell is its duality: odor molecules reach the olfactory mucosa not only orthonasally, on breathing in through the nose, but also retronasally by way of the throat, both on breathing out and when eating and drinking, mainly while swallowing (3, e2, e3). The orthonasal route is important for the perception of ambient odor molecules, the retronasal pathway for the perception of flavor (e4). Besides its function as a warning system for fire or potentially poisonous chemicals, the sense of smell also helps to detect when food has gone off. This explains why patients with olfactory dysfunction report difficulties with eating, when cooking, and in recognition of danger (e5), together with a general sense of insecurity in their daily lives, including the area of personal hygiene (4). Olfaction is also important in social interactions, e.g., in partnership and sexuality, and loss of the sense of smell can lead to social insecurity and, in approximately one third of those affected, to signs of depression (e6, e7). Olfactory dysfunction is thus frequently associated with a distinct deterioration in quality of life (e6).

**The general functions of the sense of smell**

The human sense of smell is important for the recognition of danger, perception of the flavors of food and drink, and social interaction.

**The impact of limited olfactory capacity**

Loss of the sense of smell may be associated with distinct deterioration in the quality of life and depressive symptoms.

An important role in perception of odors is played by the chemosensory system of the trigeminal nerve, which is activated by almost all odors in high concentration, triggering sensations such as stinging, pricking, tingling, coolness, warmth, or burning. Persons who lose their sense of smell or were born without it still possess this trigeminal perception.

## Learning goals

After completing this article, the reader should be able to answer the following questions:

- What are the principal causes of olfactory dysfunction?
- How can the sense of smell be measured in clinical routine?
- What are the main principles in the treatment of olfactory dysfunction?

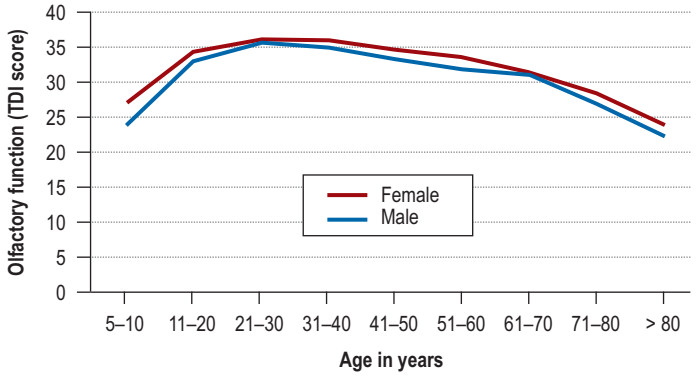
## Classification of olfactory dysfunction

Olfactory dysfunction is divided into quantitative disorders (readily measurable) and qualitative disorders (much less amenable to measurement) (5). The quantitative disorders can be subdivided by olfactory performance, e.g., according to sensitivity to odors (olfactory threshold), discrimination between odors, or identification of odors. Normal function of the sense of smell is termed normosmia (with the olfactory capacity of young adults often serving as reference value); reduction, hyposmia; and complete loss, anosmia.

Qualitative olfactory dysfunction is separated into two subgroups. The term parosmia describes disorders featuring altered perception of odors from an extant source, while phantosmia is the detection of odors in the absence of a source. As a rule, parosmia involves perception of odors as unpleasant and disgusting, e.g., coffee smells "spoilt" or "fecal." Phantosmias are often experienced as "smoky" or "burnt." These erroneous impressions are extremely disconcerting in day-to-day life. The confusing perceptions mean that parosmia and phantosmia both often seriously impair the patients' quality of life (5, 6).

Quantitative and qualitative olfactory dysfunction may occur in isolation, but are often present in combination. For example, an odor may initially trigger parosmia, followed by persisting phantosmia (e8, 8). Qualitative olfactory dysfunction is found in all causes of loss of the sense of smell and also occurs in persons with demonstrably intact olfactory capacity (normosmia) (e9). Nevertheless, an accumulation of parosmias is found in postinfectious olfactory dysfunction. Phantosmia occurs more frequently with post-traumatic olfactory dysfunction (9).

**FIGURE**




**Age-dependent change in olfactory function** in subjectively normosmic persons (n = 3355), stratified by gender (modified from [23])
TDI, Summed results, olfactory threshold + discrimination test + identification test

## The causes of olfactory dysfunction

Olfactory disorders are classified according to the underlying cause. In addition to age-related dysfunction, they are divided into conditions of acquired and congenital origin (10). Exclusive categorization of olfactory disorders as conductive or sensorineural should no longer be practiced, because, for example, olfactory dysfunction in chronic sinusitis or following an infection often features both components (11, e10).

In common with hearing and sight, human olfactory function often deteriorates with advancing age *(Figure)*. Reduced olfactory performance is found in up to 75% of persons over the age of 80 years. The underlying causes include decreased regenerative capacity of the olfactory epithelium, increased apoptosis of olfactory cells, and altered central nervous processing (12). In addition to age-related impairment there are many other causes of acquired olfactory dysfunction *(Table 1)*: it can occur after an infection of the upper respiratory tract, for instance COVID-19 (postinfectious); following craniocerebral trauma (post-traumatic); with an underlying sinunasal condition (e.g., chronic rhinosinusitis with or without nasal polyposis); in the presence of an underlying neurological or neurodegenerative disease; in association with medications or other toxic substances; after radiotherapy or surgery; and with a tumor in the frontobasal region. Olfactory dysfunction may also be classified as congenital or—after exclusion of all known causative factors—idiopathic (11).

| The classification of olfactory dysfunction | The causes of olfactory dysfunction |
|---|---|
| Reduced perception of odors is described as hyposmia, complete loss of the sense of smell as anosmia. In parosmia odors are perceived incorrectly, while in phantosmia odors are perceived in the absence of a source. | Age-related decrease in olfactory performance; chronic rhinosinusitis; following upper respiratory tract infection; craniocerebral trauma; medications; underlying neurodegenerative disease; frontobasal tumors; or idiopathic |

**TABLE 1**

**The most commonly occurring causes of acquired olfactory dysfunction in otorhinolaryngology***

| Cause | Relative frequency |
|---|---|
| **Sinunasal conditions** (inflammations of the nose and nasal sinuses, non-inflammatory respiratory disorders) | 67% |
| **Viral infection of the upper respiratory tract** | 14% |
| **Idiopathic** | 8% |
| **Trauma** | 6% |
| **Iatrogenic** | 3% |

*Modified from (10)

The congenital causes of olfactory dysfunction are divided into isolated and syndromal hyposmia and anosmia (e11). The most widely known examples of syndromal congenital anosmia are Kallmann syndrome (olfactory dysfunction together with hypogonadotropic hypogonadism) (e11) and congenital insensitivity to pain (e12, e13). Genetic variants of both isolated and syndromal congenital anosmia have been described (e14, e15). Congenital olfactory dysfunction is typically first diagnosed at 12 to 14 years of age (e16). A common radiological finding in congenital olfactory dysfunction is hypoplasia or aplasia of the olfactory bulb (e17). Suspicion of congenital olfactory dysfunction on clinical examination or imaging should prompt investigation by an interdisciplinary panel including pediatricians, endocrinologists, and, if possible, geneticists.

With regard to the neurological or neurodegenerative causes of olfactory disorders, over 90% of men and women with idiopathic Parkinson's disease (IPD) have olfactory dysfunction, which is viewed as a supportive diagnostic criterion in the clinical diagnosis of IPD. Olfactory dysfunction may occur more than 10 years before the onset of the motor symptoms (e19), so early IPD should be borne in mind as a possibility in patients with olfactory impairment of unclear origin, particularly if other non-motor symptoms are present, such as REM sleep disorders, depression, or a family history of IPD (e20, 13).

Olfactory dysfunction is found to a lesser degree in other movement disorders, e.g., multiple system atrophy, supranuclear ophthalmoplegia, and corticobasal degeneration. Only a small number of studies have so far been conducted on olfactory function in familial Parkinson's disease. Moderate hyposmia has been described in Huntington's disease (e21) and mild olfactory dysfunction in patients with hereditary ataxia (e22). Mild dysfunction has also been observed in motor neurone disease (e23).

Severe olfactory dysfunction is found in many different forms of dementia (e24, e25). Olfactory dysfunction is an early symptom of Alzheimer's disease, occurring in patients whose cognitive dysfunction is as yet only mild. Difficulty in identifying odors is a predictor of conversion to dementia (conversion rate 47%, odds ratio [OR] 5.1) (e26). Idiopathic olfactory dysfunction is often diagnosed in the prodromal phase of neurodegenerative diseases.

Olfactory dysfunction is also encountered in inflammatory disorders of the central nervous system: the incidence in multiple sclerosis is reported as 20–45% (e27). Patients with temporal lobe epilepsy tend to be affected by restriction of centrally mediated abilities such as odor identification and discrimination. Those with an acute depressive episode show a distinct reduction in olfactory sensitivity (e28), but after successful drug treatment there is no longer a significant difference from healthy persons. Limitations of the sense of smell are also known to occur in patients with schizophrenia and their first-degree relatives (e29).

## Epidemiology

The prevalence of quantitative olfactory dysfunction in the general public is around 20% (7, 14, 15). The reports range widely, however, because of the different methods used to measure olfactory performance (e30). Epidemiological studies estimate a prevalence of about 15% for olfactory dysfunction in the USA (15, e31). European studies in which olfactory performance was assessed state the prevalence of anosmia as around 5%, that of hyposmia as 15% (14, e32, e33).

The prevalence of isolated qualitative olfactory disorders is lower than that of quantitative dysfunction. While the prevalence of isolated phantosmia is assumed to be between 1% and 9%, the rate of parosmia is reported as 2–4% (e9). In contrast, parosmia occurs with much higher frequency in the context of quantitative olfactory dysfunction, depending on the cause of the dysfunction. The rate of parosmia is highest in postinfectious olfactory dysfunction (49–68%), but it is also observed in post-traumatic (14–53%), idiopathic (14–55%), and sinunasal (28–30%) dysfunction (16–19, e34). A problem with the documentation of qualitative olfactory dysfunction is that so far it has

**Epidemiology**

Reduced olfactory function is a common occurrence. The prevalence of quantitative olfactory dysfunction in the general population is around 20%, that of anosmia around 5%.

**Measurement of olfactory function**

Psychophysical assessment of olfactory function with simple screening tests for identification of odors plays a central part in the basic diagnostic work-up for olfactory dysfunction.

TABLE 2

**Swift tests for assessment of olfaction**

| Test, Author | Test type | Number of items | Reliability coefficient | Commercially available |
|---|---|---|---|---|
| **Brief Smell Identification Test (B-SIT)** Doty et al., 1996 (e75) | Identification test | 12 | 0.73 | Yes |
| **Alcohol Sniff Test** Davidson et al., 1997 (e76) | Threshold test | 1 | 0.80 | No |
| **Four-Minute Odor Identification Test** Hummel et al., 2001 (e77) | Identification test | 12 | 0.78 | Yes |
| **Quick Smell Test (Q-SIT)** Jackman and Doty, 2005 (e78) | Identification test | 3 | 0.87 | Yes |
| **Short Olfactory Screening Test** Mueller and Renner, 2006 (e79) | Identification test | 5 | 0.77 | Yes |
| **Odorized Marker Screening Test** Vodicka et al., 2007 (e80) | Identification test | 5 | Not published | No |
| **Short Connecticut Smell Test (CST)** Toledano et al., 2009 (e81) | Threshold test | 1 | Not published | No |
| **Q-Sticks Test** Hummel et al., 2010 (e82) | Identification test | 3 | Not published | Yes |
| **OLFACAT Smell Test** Mullol et al., 2015 (e83) | Identification test, questions on perception and identification | 4 | Not published | Yes |

been assessed only by questioning the persons affected.

### COVID-19-associated olfactory dysfunction

Around 50% of individuals with SARS-CoV-2-related olfactory dysfunction have loss of the sense of smell (29, e41), a rate higher than found in other viral infections (5). The loss is thought to be caused by damage to the supporting cells in the olfactory mucosa (e37), which leads indirectly to loss of function or death of the olfactory receptor neurons.

In contrast to other virus-related olfactory disorders, in COVID-19, particularly the Delta variant, nasal breathing is rarely impeded. In the Omicron variant olfactory dysfunction occurs less frequently, affecting around 15% of those infected (e40). In about 40–60% of those affected, parosmia arises several weeks or months later, especially in young patients and those with better olfactory performance. Phantosmia occurs less frequently (8).

The outcome of olfactory dysfunction in COVID-19 is thought to be generally favorable: a majority of patients report improvement within 2–3 weeks (29). Systematic investigations with psychophysical testing have shown that the initially impaired olfactory performance was much improved or restored to normal in 80–85% of patients at 6 months and in 95% at 12 months (e40). These patients are frequently regarded as fully recovered on the basis of their subjective assessments, but objective measurement often shows residual deficits (e41). Although overall the prognosis is therefore good, because of the large number of persons infected the SARS-CoV-2 pandemic has led to a significant increase in the prevalence of olfactory dysfunction. Details of the treatment of COVID-19-related olfactory dysfunction can be found in the *Box*.

## Measurement of olfaction

The quantitative determination of olfactory performance can be achieved by means of subjective assessment, psychophysical tests, or electrophysiological methods. Structural and functional imaging techniques are also used for evaluation of olfaction.

Subjective assessment is the swiftest and simplest way of estimating olfactory function and is, like the

**Detailed investigation**

For more detailed analysis of the progress of olfactory disorders, an odor identification or odor discrimination test can be accompanied by determination of the olfactory threshold. Objective depiction of olfactory function is achieved by documentation of olfactory event-related potentials.

**COVID-19-associated olfactory dysfunction**

The course of olfactory dysfunction in COVID-19 is viewed as generally favorable: most report improvement within 2–3 weeks.

BOX

### Treatment of COVID-19-associated olfactory dysfunction

If COVID-19-associated olfactory dysfunction persists, the treatment of choice is a consistent, structured program of olfactory training (10). One goal is to stimulate the regeneration of olfactory receptor neurons in the olfactory mucosa. The patient should sniff four odors, e.g., rose, lemon, eucalyptus, and cloves, twice daily for 20–30 seconds each time over a period of 4–12 months. The odors should be changed every 3–4 months (e71). There are conflicting reports on treatment with intranasal corticosteroids (32).

medical history, of great importance. However—probably owing to the variation in both burden of suffering and self-esteem—subjective ratings are imprecise and often do not correspond to the objective olfactory capacity (19, e35).

#### Psychophysical tests

Psychophysical tests of olfactory performance often evaluate three different olfactory functions (11). Threshold testing enables determination of the lowest concentration at which an odorous substance, e.g., n-butanol or phenethyl alcohol, is detected. The staircase procedure is often used for this purpose: the samples are presented repeatedly in different concentrations until the odor can confidently be distinguished from solvent (20, 21, e36, e38). The discrimination test assesses the ability to tell odors apart: the participants are given various odor triplets to sniff, with two of the samples identical and the third different. In the identification test, various odors are presented and have to be characterized using one of a list of (typically four) terms (e38). These tests are best administered in a forced-choice process, where the study participants have to give a response even if they detect no odor.

In this testing scheme the olfactory threshold tends to describe the function of the periphery of the olfactory system, while odor identification and odor discrimination rather reflect the central nervous processing of odors (5). The identification test can also be administered by the study participants themselves (e38). Numerous versions of the identification test have been developed, varying mainly in the number of different odors used, and the test has to be adapted to avoid odors unfamiliar to the region or cultural group involved (5).

It is important that the diagnostic acuity and the reliability of the tests increase with the number of odors used (22). Screening tests *(Table 2)* are limited in their ability to assess the course of olfactory function, so additional documentation of the olfactory threshold is advisable (11, 5).

The following tests, some of which are commercially available, are used worldwide: the CCCRC test, a combined threshold and identification test; the UPSIT, a single-use disposable odor identification test in different variations with three to 40 odors that can be self-administered and is therefore extremely useful in, for example, patients with acute SARS-CoV-2 infection; and the reusable Sniffin' Sticks test, which captures the olfactory threshold, odor discrimination, and odor identification *(eTable 1)*. All of these tests are of verified reliability and validity (5); for the Sniffin' Sticks, for example, there are normative data from over 9000 healthy men and women, enabling age- and gender-dependent classification of olfactory performance into normosmia, hyposmia, and anosmia (23).

It is important to use different olfactory tests in the course of COVID-19 (e40), for example, bearing in mind that odor identification may be largely normal but the olfactory threshold impaired (e41).

The determination of retronasal olfactory function (identification of aromas), however, is not an established element of routine clinical examination, although validated, reliable odor identification tests and tests for determination of the retronasal olfactory threshold are available, e.g., the "tasting powders" (e43) and the Candy Smell Test (24) *(eTable 1)*. In these tests, odorous substances are given by mouth in the form of powders or sorbitol candies and identified, analogous to orthonasal tests, from a list of options in a forced-choice model (e43, e44).

The description of qualitative olfactory dysfunction rests essentially on questioning of those affected (e45). Measurement by the SSParoT method, for example, has been proposed as a means of standardizing the severity of parosmia (e46).

#### Electrophysiological procedures and functional imaging

While psychophysical testing of olfactory performance plays a major role in daily clinical practice, objective methods are needed whenever the person's cooperation in psychophysical tests is problematic. This may be the case, for example, in children, in persons with cognitive disorders, or in the context of medicolegal investigations.

#### Measurement of the negative impact of olfactory dysfunction

Validated questionnaires on the impact on the patient's quality of life are available for documentation of the subjective severity of olfactory dysfunction and of its course.

#### Smelling tests

Tests widely available across the world are the CCCRC Test, a combined threshold and identification test; the UPSIT, a single-use odor identification test in different variations of three to 40 odors; and the reusable Sniffin' Sticks test.

Among the electrophysiological techniques, recording of olfactory event-related potentials (OERP) from the EEG has been studied closely (e47). Owing to its technical complexity, however, this method is available at only a small number of centers. Nevertheless, it is currently the only means of assessing olfactory function objectively.

In contrast, magnetic resonance imaging (MRI) is widely available and enables the structural examination of areas of the brain that are intimately involved with the processing of odors, such as the olfactory bulb and the orbitofrontal cortex (25). In these structures, for example, small volumes point to the presence of a reduction in olfactory capacity. With the aid of imaging, a possible prognosis can then be outlined (e48). Cranial MRI naturally also clarifies whether, for instance, an intracranial tumor such as olfactory nerve meningioma is present that could cause olfactory dysfunction (e49). Not only structural MRI but also functional olfactory MRI can be performed (e50); however, the results at individual level are difficult to interpret (e51).

## Measurement of the detrimental effect of olfactory dysfunction

Olfactory dysfunction can have a negative impact on the quality of life. This can hardly be assessed by psychophysical tests but is instead ascertained with the aid of questionnaires. One instrument often used to evaluate the olfaction-specific quality of life is the Questionnaire of Olfactory Dysfunction (QOD) with 52 items (26, e52). A short version with seven questions is also available (27).

Retronasal perception of odors has a greater influence on the quality of life than orthonasal detection (e53, 28). Other questionnaires, such as the Importance of Olfaction Questionnaire, measure the individual significance of the sense of smell (e54), which decreases with increasing age and with the increasing duration of olfactory dysfunction (28, e54).

## The prognosis of olfactory dysfunction

Olfactory disorders may become less marked (e55) and may, as seen for example in COVID-19-associated dysfunction, disappear entirely (e56, 29).

The prognosis of and spontaneous recovery from olfactory dysfunction depends on, among other factors, the duration of the dysfunction, its cause, the presence/absence of parosmia at initial examination, the patient's smoking status, and, most important, their age (e57, e58). The prognosis is therefore most favorable in younger non-smokers with a postviral olfactory disorder, relatively good olfactory function, only brief loss of olfactory function, and parosmic changes (17).

Among patients whose loss of the sense of smell persists for a longer period, e,g., 18 months, only around 30% will experience a spontaneous clinically relevant improvement in olfactory performance within 12 months (e59).

## Treatment

While for patients with olfactory dysfunction in connection with sinunasal conditions it is recommended that the underlying disease be treated (e60), there are few therapeutic options and recommendations for olfactory disorders of other causes (7, e61).

Although many different kinds of treatment have been tested in clinical studies, apart from management of the inflammatory disease only olfactory training, i.e., the deliberate sniffing of various odors several times each day, possesses proven therapeutic value (5).

### Drug treatment of sinunasal olfactory dysfunction

Topical corticosteroids form the basis of treatment (11, e60, e62) (evidence: *eTable 2*). They not only ameliorate the underlying chronic inflammation, e.g., rhinosinusitis with nasal polyposis, but also have a significant effect on olfactory function (10). Systemic steroids are given only for a short time to confirm the diagnosis of inflammation-related olfactory dysfunction and reduce the inflammation before continuing with topical treatment (e63) (evidence: eTable 3). The review and meta-analysis by Banglawala et al. (e64) included 28 randomized controlled trials (RCT) of topical and systemic corticoid therapy. Meta-analysis of the latter (five studies) showed significant improvement of both subjective (SMD −2.22, 95% confidence interval [−3.94; −0.49]) and objective (SMD 0.65 [0.28; 1.01]) olfactory function compared with placebo. As for topical treatment, 70% of the studies reviewed found improvement. When giving topical therapy, it is advisable to administer the nasal spray using a long applicator (e63, e65). With a normal applicator, the filtering function of the nose practically prevents the spray from reaching the olfactory cleft (e66, e67). The same effect can be achieved by administering the nasal drops in the so-called Kaiteki position (https://goo.gl/ZqxhDN) (e68). Corticosteroids are currently recommended only for sinunasal causes (5, e60).

Various monoclonal antibodies ("biologics") have recently been approved for the treatment of rhinosinusitis

**Treatment of sinunasal olfactory dysfunction**

Treatment of the underlying inflammatory disease is recommended.

**Treatment of postviral, post-traumatic, and idiopathic olfactory dysfunction**

To date, the only treatment option is olfactory training: sniffing various odors several times each day.

with nasal polyposis. Because of their specific action on the inflammation they also exert a positive effect on the associated olfactory dysfunction (30), but they are not licensed for the treatment of olfactory dysfunction alone.

### Olfactory training

Olfactory training has become established as the treatment of choice for non-sinunasal olfactory dysfunction (7, e69) (evidence: *eTable 4*). A meta-analysis (e70) of 13 RCT featuring very heterogeneous groups revealed a strong association for the improvement of odor identification (g = 0.83), odor discrimination (g = 0.89), and overall olfaction (g = 1.10), together with a mild to moderate effect for the olfactory threshold (g = 0.34). Olfactory training should be carried out carefully and consistently, smelling four different odors for 30 seconds each twice daily over a period of 4–6 months or longer. The effect is even better if the odors are replaced by different ones after 3 months (e71). Studies have shown that the initial olfactory performance and the cause of the olfactory dysfunction are associated with achievement of a relevant improvement in olfactory function after the training (e72, e73, 31). A less pronounced improvement is found for olfactory dysfunction of post-traumatic or idiopathic origin.

### Further treatment options

Other topical treatments that have been evaluated are sodium citrate, vitamin A drops, theophylline, palmitoyl ethanolamide/luteolin, and platelet-rich plasma. The systemic treatments that have been investigated include zinc, pentoxifylline, theophylline, cavoverin, α-lipoic acid, and vitamin B (e61, e74). Acupuncture has also been used to treat olfactory dysfunction (e74). Although many of these treatment options showed positive effects in the initial case series, as a rule there is a lack of robust clinical trials, particularly RCT and meta-analyses—although isolated RCT have been carried out for, among others, theophylline, vitamin A, and α-lipoic acid (5, 11).

**Conflict of interest statement**

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**Drug treatment of sinunasal olfactory dysfunction**

Topical corticosteroids are the basic treatment. They not only ameliorate the underlying chronic inflammatory condition but also have a significant effect on olfactory function.

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▶ **Supplementary material**

**eReferences, eTables, eCaseReport:**
**www.aerzteblatt-international.de/m2022.0411**

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Only one answer is possible per question. Please select the answer that is most appropriate.

### Question 1

**What is the rate of olfactory dysfunction among patients with idiopathic Parkinson's disease?**

a) 10%
b) 20%
c) 30%
d) 50%
e) 90%

### Question 2

**Which of the following nerves has a major influence on olfaction?**

a) The ophthalmic nerve
b) The mandibular nerve
c) The abducens nerve
d) The facial nerve
e) The trigeminal nerve

### Question 3

**What is parosmia?**

a) The perception of smells in the absence of an odor source
b) Reduced olfactory capacity
c) Qualitatively altered perception of smells
d) Hyperactive olfaction
e) Faulty osmosis

### Question 4

**Which of the following is the principal determinant of perceived aroma?**

a) The surface of the tongue
b) The composition of the salivary fluid
c) The dental status
d) Retronasal olfaction
e) The alignment of the nasal septum

### Question 5

**What is the prevalence of anosmia in the general population?**

a) 0.2%
b) 5%
c) 10%
d) 20%
e) 40%

### Question 6

**In what type of olfactory dysfunction is the rate of parosmia highest?**

a) In post-traumatic olfactory dysfunction
b) In postinfectious olfactory dysfunction
c) In sinunasal olfactory dysfunction
d) In idiopathic olfactory dysfunction
e) In congenital olfactory dysfunction

### Question 7

**Which of the following is a promising treatment option for post-traumatic olfactory dysfunction?**

a) Antibiotics
b) Nasal sprays containing corticoids
c) Regular olfactory training for at least 6 months
d) Saline nasal rinses
e) Realignment of the septum

### Question 8

**What is tested using Sniffin' Sticks?**

a) The subjective assessment of olfactory function
b) The smell-related quality of life
c) Olfactory event-related potentials
d) The threshold, discrimination, and identification of odors
e) The assessment of nasal breathing

### Question 9

**At what age is olfactory function best?**

a) 5–10 years
b) 21–30 years
c) 41–50 years
d) 61–70 years
e) Over 80 years

### Question 10

**Which of the following olfactory dysfunctions is generally treated with topical or systemic corticoids?**

a) Post-traumatic olfactory dysfunction 2 years after the causative event
b) Chronic rhinosinusitis with nasal polyposis
c) Congenital anosmia
d) Olfactory dysfunction in connection with COVID-19
e) Olfactory dysfunction following chemotherapy

► **Participation is possible only via the Internet: cme.aerzteblatt.de**

**Supplementary material to:**

# Olfactory Dysfunction: Etiology, Diagnosis, and Treatment

by Thomas Hummel, David T. Liu, Christian A. Müller, Boris A. Stuck, and Antje Welge-Lüssen, Antje Hähner

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## CASE REPORT

A 46-year-old man who worked as a self-employed retailer presented with olfactory dysfunction of approximately 3 years' standing. He reported that the dysfunction had developed gradually and that he had hardly noticed it at first. He denied possible causes such as an infection, trauma, or medications, and no comorbidities, difficulty in nose breathing, or any other nasal problems were present. ENT examination including nasal endoscopy found no abnormalities. Investigation of orthonasal olfactory function using the Sniffin' Sticks procedure, comprising threshold, discrimination, and identification tests, revealed functional anosmia. Suprathreshold concentrations of tasting powders in the primary flavors were correctly identified, showing normogeusia. As the findings of magnetic resonance imaging were normal, the diagnosis was idiopathic functional anosmia. Regular olfactory training was recommended. Due to the absence of symptoms, no neurological investigations took place.

The anosmia remained unchanged over the course of several follow-up visits. At 3 years after diagnosis the patient reported the recent onset of tremors in the left extremities at rest, together with minor clumsiness of the left hand and occasional pain in the right thigh. Clinical examination by a neurologist found slight, moderately frequent trembling of the left extremities at rest, slight left-sided bradydiadochokinesis, discrete rigor of the left arm, and reduced left arm swing. The diagnosis was suspected idiopathic Parkinson's disease and the patient was transferred to the department of neurology for further investigation.

**eTABLE 1**

**Comprehensive tests for assessment of olfaction**

| Test, author | Test type | Number of items | Reliability coefficient | Commercially available |
|---|---|---|---|---|
| **Connecticut Chemosensory Clinical Research Center (CCCRC) Test**<br>Cain et al., 1983 (21) | Threshold, identification | 1<br>10 | Threshold: 0.68<br>Identification: 0.60 | No |
| **University of Pennsylvania Smell Identification Test (UPSIT)**<br>Doty et al., 1984 (e84) | Identification | 40 | 0.94 | Yes |
| **T&T Olfactometer**<br>Toyota et al.,1978 (e85) and Takagi, 1989 (e86) | Threshold, identification | 5 | Threshold: 0.56–0.71<br>Identification: 0.33–0.45 | Yes |
| **Sniffin' Sticks Test**<br>Hummel et al., 1997 (e87) | Threshold, discrimination, identification | 16 per subtest | 0.72 | Yes |
| **Tasting powders**<br>Heilmann et al., 2002 (e43) | Retronasal identification | 20 | 0.76 | No |
| **European Test of Olfactory Capabilities (ETOC)**<br>Thomas-Danguin et al., 2003 (e88) | Threshold, identification | 16 | 0.90 | No |
| **Barcelona Smell Test**<br>Cardesin et al., 2006 (e89) | Odor perception, identification, odor memory | 24 | Not published | No |
| **Candy Smell Test**<br>Renner et al., 2009 (24) | Retronasal identification | 23 | 0.75 | No |
| **Extended Sniffin' Sticks Test**<br>Haehner et al., 2009 (e90) | Threshold, discrimination, identification | 32 | 0.93 | Yes |
| **Sniffin' Test of Odor Memory (TOM)**<br>Croy et al., 2015 (e91) | Odor memory | 8 | 0.70 | Yes |

**eTABLE 2**

**Evidence for treatment with intranasal topical corticoids in sinunasal olfactory dysfunction caused by chronic rhinosinusitis with polyposis (RCT)**

| Author | Study participants | Clinical endpoint | Results |
|---|---|---|---|
| **Xu et al.,** 2020 (e92) | n = 127<br>1) Methylprednisolone 24 mg + budesonide NS for 1 week<br>2) Budesonide nasal drops + budesonide NS for 1 week<br>3) Budesonide NS for 1 week | VAS (0–10) | Significant VAS improvement in all groups compared with baseline<br>No difference between the groups |
| **Zeng et al.,** 2019 (e93) | n = 187*<br>1) Fluticasone propionate NS for 3 months<br>2) Clarithromycin 250 mg for 3 months | VAS (0–10) | Significant VAS improvement in both groups compared with baseline<br>No difference between the groups |
| **Khan et al.,** 2019 (e94) | n = 310<br>1) Mometasone furoate NS 1/d<br>2) Mometasone furoate NS 2/d<br>3) Placebo | Subjective assessment (0–3) | Significant improvement compared with baseline only for 2 × daily nasal spray |
| **Zhou et al.,** 2016 (e95) | n = 748<br>1) Mometasone furoate NS 2/d for 16 weeks<br>2) Placebo mometasone furoate | Subjective assessment (0–3) | Significant improvement compared with placebo |
| **Bangwala et al.,** 2014 (e64) | n = 419<br>Review: 28 RCT<br>Meta-analysis: 5 RCT | Subjective assessment (0–3)<br>Objective testing | Significant improvement of olfaction by oral and topical steroids (improvement in 70% of the topical studies) |
| **Jankowski et al.,** 2009 (e96) | n = 246<br>1) Fluticasone propionate NS 2/d for 8 months<br>2) Fluticasone propionate NS 2/d for 1 month, Fluticasone propionate NS 1/d + placebo NS for 7 months<br>3) Placebo NS for 2 months, then fluticasone propionate NS 2/d for 6 months | VAS (0–100)<br>Mean sense of smell disorder score | Significant improvement of both scores in corticoid groups compared with placebo |
| **Ehnhage et al.,** 2009 (e97) | n = 68<br>1) Fluticasone propionate nasal drops for 10 weeks<br>2) Placebo for 10 weeks | Subjective assessment (0–3)<br>Butanol threshold test | No significant improvement compared with placebo |
| **Small et al.,** 2008 (e98) | n = 447<br>1) Mometasone furoate NS for 4 months<br>2) Placebo | Subjective assessment (0–3) | Significant improvement compared with placebo |

*Also included patients who had chronic rhinosinusitis without polyposis
NS, Nasal spray; RCT, randomized controlled trial; VAS, visual analog scale

**eTABLE 3**

**Evidence for treatment with oral corticoids in sinunasal olfactory dysfunction caused by chronic rhinosinusitis with polyposis (RCT)**

| Author | Study participants | Clinical endpoint | Results |
|---|---|---|---|
| **Papadakis et al.,** 2021 (e99) | n = 140<br>1) Dexamethasone for 7 days + 12 weeks budesonide NS<br>2) Budesonide NS for 12 weeks | VAS (0–10)<br>Sniffin' Sticks identification test | Significant improvement in VAS and identification test compared with solely topical administration of steroids |
| **Ecevit et al.,** 2015 (e100) | n = 22<br>1) Prednisolone 60 mg/d for 7 days, then dose reduction up to day 16<br>2) Placebo | VAS (0–10)<br>Butanol threshold | Significant improvement in VAS and threshold test compared with placebo |
| **Banglawala et al.,** 2014 (e64) | n = 419<br>Review: 28 RCT<br>Meta-analysis: 5 RCT | Subjective assessment<br>Objective testing | Significant improvement of olfactory capacity by oral (subjective: SMD −2.22, 95% CI [−3.94; −0.49]; objective: SMD 0.65, 95% CI [0.28; 1.01] and topical steroids |
| **Alobid et al.,** 2014 (e101) | n = 92<br>1) Prednisone 30 mg for 12 weeks + budesonide NS for 12 weeks<br>2) No steroids | Barcelona Smell Test | Significant improvement compared with baseline only in oral prednisone group |
| **Kirtsreesakul et al.,** 2012 (e102) | n = 114<br>1) Prednisolone 50 mg for 2 weeks + mometasone furoate NS for 10 weeks<br>2) Placebo for 2 weeks + mometasone furoate NS for 10 weeks | Subjective assessment (0–3) | Significant improvement compared with baseline only in oral prednisone group |
| **Vaidyanathan et al.,** 2011 (e103) | n = 60<br>1) Prednisolone 25 mg for 2 weeks + topical steroids for 26 weeks<br>2) Placebo for 2 weeks + topical steroids for 26 weeks | VAS (0–100)<br>Pocket Smell Test (PST) | Significant improvement in VAS and PST compared with placebo |
| **Van Zele et al.,** 2010 (e104) | n = 47<br>1) Methylprednisolone 32 mg for 20 days<br>2) Placebo for 20 days | VAS (0–10) | Significant improvement in VAS compared with placebo |
| **Benitez et al.,** 2006 (e105) | n = 84<br>1) Prednisone 30 mg for 2 weeks + budesonide NS for 10 weeks<br>2) No steroids | Subjective assessment (0–3) | Significant improvement compared with baseline only in oral prednisone group |
| **Wright et al.,** 2007 (e106) | n = 26<br>1) Prednisone 30 mg for 2 weeks + ESS<br>2) Placebo + ESS | VAS (0–10) | Significant improvement compared with baseline only in oral prednisone group |
| **Hissaria et al.,** 2006 (e107) | n = 40<br>1) Prednisolone 50 mg for 2 weeks<br>2) Placebo for 2 weeks | Modified 31-item Rhinosinusitis Outcome Measure Questionnaire | Significant improvement compared with baseline only in oral prednisone group |

ESS, Endoscopic sinus surgery; NS, nasal spray; RCT, randomized controlled trial; VAS, visual analog scale

**eTABLE 4**

**Evidence for the efficacy of olfactory training in the treatment of olfactory dysfunction**

| Author | Design | Study participants | Clinical endpoint | Results |
|---|---|---|---|---|
| **Pieniak et al.,** 2022 (e108) | Review | n = 3134<br>(PIOD, PTOD, IOD, sinunasal, IPD, medication, elderly)<br>Review: 48 studies | Sniffin' Sticks or other psychophysical tests | Improvement of olfactory function in all patient groups except for sinunasal etiology, greatest efficacy for discrimination and identification |
| **Yaulaci et al.,** 2022 (e109) | Prospective, non-randomized study | n = 51 (PIOD)<br>1) Olfactory training<br>2) No treatment for 12 weeks | Sniffin' Sticks | Clinically significant improvement in 40% of training group versus 6% of control group |
| **Lechner et al.,** 2022 (e110) | RCT | n = 63 (PIOD)<br>1) Olfactory training<br>2) No treatment for 12 weeks | Brief Smell Identification Test (BSIT) | Non-significant improvement of BSIT score in training group versus control group, OR 2.38 |
| **Choi et al.,** 2021 (e111) | Prospective, non-randomized study | n = 104 (PIOD)<br>1) Olfactory training<br>2) No treatment for 3 months | Sniffin' Sticks | Significant improvement of TDI, threshold, and identification in training group |
| **Qiao et al.,** 2020 (e112) | RCT | n = 125 (PIOD)<br>1) Olfactory training<br>2) Training with household odors (e.g., perfume, vinegar) for 24 weeks | Sniffin' Sticks | Significant improvement of TDI, discrimination, and identification in both groups |
| **Saatci et al.,** 2020 (e113) | RCT | n = 60 (PIOD)<br>1) Olfactory training (4 odors)<br>2) Training ball with 4 odors for 12 weeks | Sniffin' Sticks | Significant improvement of TDI, discrimination, and identification in both groups |
| **Kattar et al.,** 2020 (e114) | Systematic review and meta-analysis | n = 990 (PIOD)<br>Review: 16 studies; meta-analysis: 4 studies | Sniffin' Sticks | Significant improvement in all studies, OR 2.77 |
| **Sorokowska et al.,** 2017 (e70) | Systematic review and meta-analysis | n = 1005 (PIOD, PTOD, IOD, sinunasal, IPD, elderly)<br>Meta-analysis: 13 studies | Sniffin' Sticks | Significant association between training and improvement of TDI (g = 1.10), discrimination (g = 0.89) and identification (g = 0.83) |
| **Pekala et al.,** 2016 (e115) | Systematic review and meta-analysis | n = 639 (PIOD, PTOD, IOD, sinunasal, IPD, elderly)<br>Review: 10 studies; meta-analysis: 3 studies | Olfactory improvement using psychophysical tests | Significant association between training and improvement of TDI, discrimination, and identification, OR 2.75 |
| **Jiang et al.,** 2019 (e116) | RCT | n = 111 (PTOD)<br>1) Olfactory training (4 odors)<br>2) Olfactory training (1 odor – PEA) for 6 months | UPSIT<br>PEA threshold | Significant improvement of PEA threshold in both groups, UPSIT improvement only in PEA group |
| **Langdon et al.,** 2018 (e117) | RCT | n = 42 (PTOD)<br>1) Olfactory training (6 odors)<br>2) No treatment for 12 weeks | Barcelona Smell Test<br>Butanol threshold test<br>VAS | Significant improvement in training group compared with control group for threshold test; no change in VAS, Barcelona Smell Test |
| **Oleszkiewicz et al.,** 2018 (e118) | RCT | n = 108 (PIOD, IOD)<br>Olfactory training with<br>1) 4 odors<br>2) 4 odor combinations<br>3) 3 × 4 odors, changed every 2 months | Sniffin' Sticks | Significant improvement of TDI, threshold, and identification in all groups, no effect of training procedure |
| **Patel et al.,** 2017 (e119) | RCT | n = 43 (PIOD, IOD)<br>1) Olfactory training (4 odors)<br>2) No treatment for 6 months | UPSIT | Significant in 32% of the training group (versus 13% in control group) |

| | | | | |
|---|---|---|---|---|
| **Damm et al.,** 2014 (e72) | RCT | n = 171 (PIOD)<br>1) Olfactory training with high-concentration odors<br>2) Olfactory training with low-concentration odors<br>Cross-over after 18 weeks | Sniffin' Sticks | Significant improvement of TDI in 26% of the training group with high-concentration odors<br>(versus 15% in group with low-concentration odors ) |
| **Poletti et al,** 2017 (e120) | Prospective,<br>pseudo-randomized study | n = 96 (PIOD, PTOD)<br>Olfactory training with<br>1) 4 high-molecular odors<br>2) 4 low-molecular odors for 5 months | Sniffin' Sticks | Significant improvement of TDI in both groups,<br>high-molecular odors associated with significantly better threshold in PIOD |
| **Konstantinidis et al.,** 2016 (e121) | Prospective,<br>partially randomized study | n = 111 (PIOD)<br>1) Olfactory training for 16 weeks<br>2) Olfactory training for 56 weeks<br>3) No treatment | Sniffin' Sticks | Significant improvement of TDI in<br>training groups compared with controls;<br>highest increase in long-term group<br>( 9.1 for 16 weeks, 11.4 for 56 weeks) |
| **Gellrich et al.,** 2018 (e122) | Prospective cohort study | n = 30 (PIOD)<br>1) Olfactory training for 12 weeks | Sniffin' Sticks<br>Gray matter (GM) volume on MRI | Significant improvement of TDI and significant<br>GM volume increase in hippocampus, thalamus, and cerebellum |
| **Hummel et al.,** 2018 (e123) | Prospective cohort study | n = 23 (PIOD, IOD)<br>1) Olfactory training for 4–6 months | Sniffin' Sticks<br>EOG | Significant improvement in identification, but not in TDI<br>EOG response significantly improved by training |
| **Altundag et al.,** 2015 (e71) | Prospective cohort study | n = 85 ( PIOD)<br>1) Olfactory training with 3 sets of 4 odors<br>2) Olfactory training with 4 odors<br>3) No treatment for 36 weeks | 1) Sniffin' Sticks<br>2) VAS | Significant improvement of TDI in<br>training groups compared with controls, with greatest improvement rate in group with changing odors (TDI 8.2 versus 6.1 versus 1.7) |
| **Konstantinidis et al.,** 2013 (e73) | Prospective cohort study | n=119 (PTOD, PIOD)<br>1) Olfactory training (4 odors)<br>2) No olfactory training for 4 months | Sniffin' Sticks | Significant improvement of TDI in<br>training groups compared with controls,<br>particularly in PIOD (TDI 6.25 versus 1.5 PIOD, 5.1 versus 1.2 PTOD) |
| **Haehner et al.,** 2013 (e124) | Prospective cohort study | n = 70 (PD)<br>1) Olfactory training<br>2) No training | Sniffin' Sticks | Significant improvement of TDI and<br>discrimination in training group compared with controls (TDI by 2.4 versus −0.6) |
| **Hummel et al.** 2009 (e125) | Prospective cohort study | n = 56 (PIOD, PTOD, IOD)<br>1) Olfactory training<br>2) No treatment for 12 weeks | Sniffin' Sticks | Significant improvement of TDI and olfactory threshold in training group compared with controls |

EOG, Electro-olfactogram; IOD, idiopathic olfactory dysfunction; IPD, idiopathic Parkinson's disease; PIOD, postinfectious olfactory dysfunction; PTOD, post-traumatic olfactory dysfunction; RCT, randomized controlled trial; TDI, summed score olfactory threshold + discrimination test + identification test; UPSIT, University of Pennsylvania Smell Identification Test