Olfaction and Anosmia in Rhinosinusitis

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Olfactory disorders can cause serious consequences from the inability to detect many olfactory warning signals (eg, smoke, spoiled food, and gas leaks) and can significantly impact nutritional status, eating satisfaction, and many other issues related to quality of life. More than 200,000 people a year seek treatment for impaired olfactory ability, and available evidence suggests this figure is a significant underestimate of those affected. Rhinitis and rhinosinusitis are the primary etiologies for olfactory loss or distortion among patients presenting to chemosensory clinics, and they are among the most common chronic medical conditions in the United States, affecting an estimated 33 million people. Both allergic and nonallergic rhinitis/rhinosinusitis can result in diminished, distorted, or absent olfactory ability. Current therapies are only partially or transiently effective in reversing olfactory loss. The underlying mechanisms by which rhinitis/rhinosinusitis impact olfactory ability are likely to be multifactorial and might include altered air flow and odor deposition, changes in mucus composition, and effects of inflammatory mediators on receptor cell differentiation, maturation, or function.

Introduction

Among patients presenting to chemosensory clinics for diagnosis, rhinitis and/or rhinosinusitis are the most frequent causes of olfactory impairment [1] and the most common chronic medical conditions in the United States, affecting an estimated 32 million people per year [2,3]. Therefore, a substantial number of individuals are at risk for being unable to detect many olfactory warning cues (*eg*, natural gas, harmful chemicals) and incur decreases in their quality of life from an inability to experience food flavors and fragrances [4].

Rhinitis and/or rhinosinusitis have the potential to impair olfactory ability in several ways. Inflammation-induced constriction of the airway can alter or impede airflow through the nasal cavity, reducing access of volatile compounds to the sensory receptor cells, which are located in a relatively protected area of the nasal passages (Fig. 1). Changes in the composition and transport of the aqueous mucus layer through which the odorants must diffuse can impair access to or removal from the receptor sites. Proteins secreted by the infiltrating cells of the immune system might directly injure or modulate the function of olfactory receptor neurons or other cells within the neuroepithelium. Fibrosis or edema might change the structure of the epithelium or submucosa, impeding axonal outgrowth and preventing successful regeneration of the neuroepithelium. Any of these mechanisms have the potential to impact olfactory perception. Unfortunately, currently available treatments for rhinitis-induced olfactory disorders are ineffective in a significant proportion of patients, frequently do not provide more than temporary recovery of olfactory function, and might offer significant risk (*eg*, chronic oral steroids or surgery).

The goal of this paper is to review the features of olfactory dysfunction and the effects of rhinitis/rhinosinusitis on olfactory acuity and perception. Although few treatments have been found to mitigate olfactory loss secondary to rhinitis, as more is understood about the underlying factors that contribute to olfactory loss, it is hoped that more effective treatments can be identified.

Characterization of Rhinitis and Rhinosinusitis

Rhinitis is a heterogenous inflammatory response of the nasal mucosa [5], diagnosed primarily on the basis of etiology (allergic, nonallergic, infectious) and characterized by specific nasal symptomatology (*eg*, rhinorrhea, sneezing, itching, and postnasal drainage) [6]. Rhinosinusitis is an inflammatory response in the nasal and sinus mucosa, fluids, and underlying tissues, and is also diagnosed on the basis of specific symptomatology (Table 1). Rhinitis and rhinosinusitis can occur in both acute and chronic forms. Chronic rhinosinusitis is defined as prolonged rhinosinusitis symptoms that persist for more than 12 weeks, coupled with changes in opacity on CT scans that remain unresolved in the absence of infection. Differentiating between an allergic and nonallergic etiology is obviously critical for developing appropriate treatment strategies, but is also of importance for understanding the potential impact on olfaction. Although both types of rhinitis can

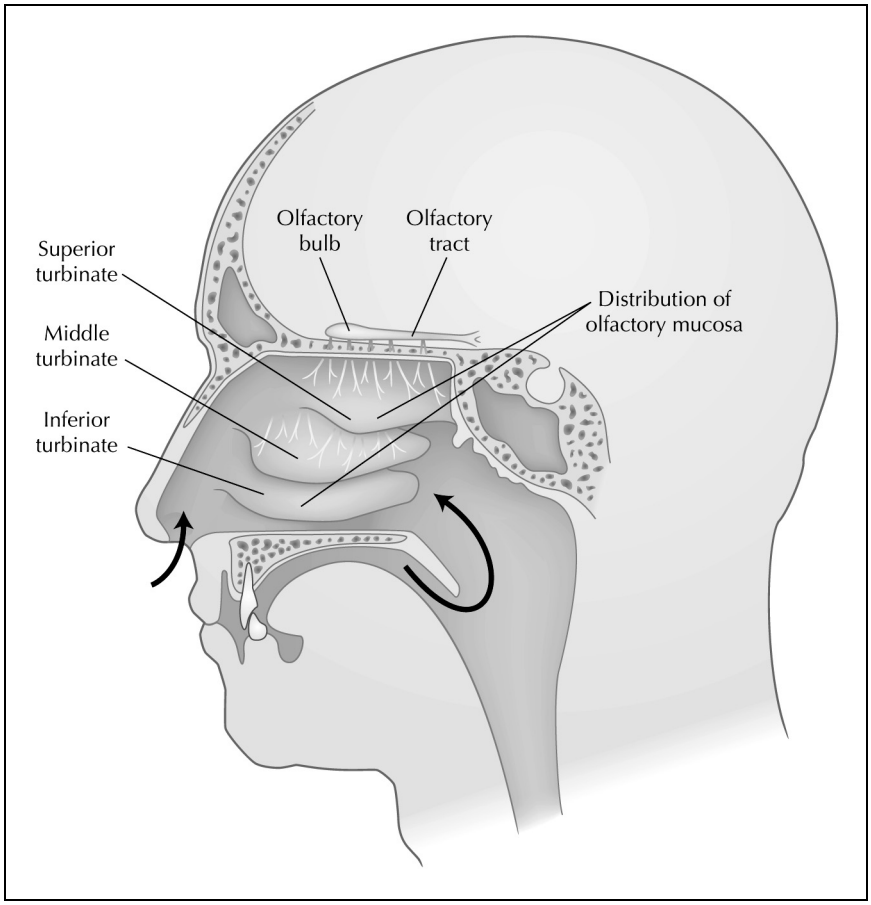

Figure 1. Anatomy of the nasal passages, showing the turbinates, the location of the olfactory epithelium, and orthonasal and retronasal odorant flow (*arrows*).

lead to impaired olfactory acuity, studies suggest that nonallergic rhinitis results in more prevalent and more severe olfactory deficits than does allergic rhinitis [7,8].

Anatomy of Olfaction

Many of the anatomical features of the human nasal passages and their role in the process of olfactory perception render this sensory system susceptible to disruptions from conditions that impact airflow and mucosal integrity. The nasal cavity can be divided into three parts: the nasal vestibule, the respiratory region, and the olfactory region. The septum, consisting of a bony plate and a cartilaginous wall, divides the nasal cavity into two symmetric halves. On average, in humans, the total surface area of both nasal cavities is approximately 150 cm^2, and the total volume approximately 15 mL. The anterior portion of the nasal cavity opens in the nostril, whereas the posterior part opens into the rhinopharynx. Volatile chemicals can be inhaled into the nasal cavity orthonasally through the nostril (or nares) or can enter retronasally from the mouth or during swallowing (thus enabling the significant contribution of olfactory perception to food flavor). During orthonasal olfaction, the odor plumes are broken up by convolutions in the tissue, called turbinates (Fig. 1). Actual exposure to odorants (and thus, olfactory perception) depends on patterns of airflow through a geometrically complex structure, diffusion through the aqueous mucus layer, and signal transduction processes that occur within the olfactory receptor neurons and the olfactory bulb. Rhinitis/rhinosinusitis can potentially impair olfaction at any or all of these stages.

Clinical Assessment of Olfactory Dysfunction

Most cases of olfactory dysfunction appear to arise from three primary causes: 1) chronic rhinitis/rhinosinusitis (~30%), which might lead to generalized inflammatory processes that can change the composition of the mucus in the olfactory epithelium or, alternatively, through edema, can change the patterns of airflow and odorant deposition [1]; 2) acute viral rhinitis (14%–26%) [1,9] that might result in viral damage to peripheral olfactory receptors [10]; and 3) head trauma (10%–19%) [1], which is generally due to tearing or severing of the olfactory neuron axons where they pass through the cribriform plate.

Olfactory dysfunction associated with or secondary to rhinosinusitis can take several forms. Three classifications of olfactory disorders have been described: anosmia (the total absence of olfaction); hyposmia (diminished sensitivity of olfaction); and dysosmia (quality distortion of normal olfaction). Two subcategories of dysosmia include phantosmia (perception of an unpleasant smell when none is present) and parosmia (the perception of a dis-

Table 1. Factors associated with the diagnosis of rhinosinusitis

Major factors	Minor factors
Facial pain/pressure*	Headache
Nasal obstruction/blockage	Fever (all nonacute)
Nasal discharge/purulence/ postnasal drainage	Halitosis
Hyposmia/anosmia	Fatigue
Purulence in nasal cavity on examination	Dental pain
	Cough
Fever (acute rhinosinusitis only) **	Ear pain/pressure/ fullness

* Facial pain/pressure alone does not constitute a suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign.
** Fever in acute rhinosinusitis alone does not constitute a strongly suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign.

torted odor in response to a particular stimulus). In addition, rhinitis or rhinosinusitis can differentially impair orthonasal versus retronasal olfactory acuity. Comparisons of orthonasal and retronasal olfactory performance in patients with chronic rhinitis/rhinosinusitis (CR) have found that a significant proportion of patients having normal orthonasal olfactory perception exhibit profound decrements in retronasal olfactory perception.

The chemosensory clinical research centers funded by the National Institutes of Health have established criteria for olfactory dysfunction that rely on the measurement of odor detection thresholds for one or more chemicals (*eg*, butanol, pyridine, phenylethyl alcohol) and performance on a multiple-item odor identification task [1,11,12]. These measures employ a forced-choice format with a limited number of response alternatives and are, therefore, less prone to subjective biases and variability than are scaling measures or questionnaires. The need for objective test methods is particularly critical in assessing olfactory disorders. Because olfactory impairment due to CR often occurs gradually and might be unilateral, the patient might not notice and/or report significant changes in perceptual acuity until the dysfunction becomes severe [13,14],

The use of a battery of tests can greatly assist in identifying the nature of the olfactory problem. For example, hyposmia (partial loss) can be distinguished from anosmia (total loss) and quantified by measuring sensitivity at threshold for one or more chemicals. In contrast, odor identification serves as a global assessment tool, providing information on the ability to perceive olfactory stimuli, discriminate qualities, and associate the proper verbal label with an odor. A careful selection of response alternatives can provide insight into the nature of the errors made by subjects, such that inclusion of a near-miss alternative can serve to confirm a diagnosis of hyposmia (diminished olfactory ability) versus anosmia (loss of olfactory ability), whereas normal threshold sensitivity coupled with poor identification performance and complaints about odor distortions can verify the presence of dysosmia [1]. In addition, although it has often been assumed that olfactory loss is homogeneous across odorants, one study in which an odorant confusion matrix was used to assess olfactory function suggested that misidentification of r-carvone (spearmint odor) was more common for chronic rhinosinusitis/polyposis patients than for those with less severe conditions [15]. Therefore, a comprehensive test battery, including a variety of different odorants, might be necessary to fully realize the impact of rhinitis/rhinosinusitis on olfactory function.

Olfactory Dysfunction in Rhinitis/Rhinosinusitis

Acute viral rhinitis can result in both a temporary and permanent loss of olfaction. However, permanent impairment of olfaction occurs less frequently than temporary impairment and is significantly more prevalent among the elderly, who have likely sustained more cumulative damage to the olfactory epithelium, suggesting that the loss of olfaction following acute viral rhinitis might be due to factors other than congestive changes impeding airflow. Although only a few studies have quantitatively evaluated olfactory function following viral rhinitis, two have shown olfactory impairment. Akerlund *et al.* [16] found elevated olfactory thresholds to 1-butanol among volunteers who had been inoculated with coronavirus (4 days prior), relative to uninfected control subjects. In this study, the magnitude of olfactory impairment was correlated with the degree of nasal congestion.

A second study evaluated patients shortly after they experienced the natural onset of acute viral rhinitis and found that decreased anterior airway volume and increased mucus secretion were correlated with olfactory perception (*ie*, elevated odor thresholds, decreases in perceived odor intensity, and decreased cortical response to olfactory stimuli) [17]. Although administration of oxymetazoline decreased mucus secretion and increased airway volume among this cohort, it had no impact on recovery of olfactory function. This finding raises the possibility that, in some cases, the olfactory impairment that occurs subsequent to acute viral rhinitis might be due to mechanisms other than nasal congestion.

Although still relatively few in number, investigations of the impact of chronic rhinitis/rhinosinusitis on olfactory function have provided the strongest evidence that inflammatory mechanisms can significantly impair olfactory ability. Cowart *et al.* [18] conducted a well-controlled study of olfactory function in allergic rhinitis evaluating sensitivity to the odorant phenylethyl alcohol (rose) to document olfactory loss, and they compared the findings with clinical and radiographic data and nasal airway resistance for both atopic patients and nonatopic controls. Detection thresholds were significantly elevated for patients compared with controls (23.1% of allergic rhinitics exhibited clinically significant olfactory decrement); this loss was associated with the presence of rhinosinusitis or nasal polyps. Interestingly, however, measures of total airway resistance did not correlate with

olfactory performance, again raising the possibility that: 1) congestion is not the only factor in rhinitis-induced olfactory disorders; or 2) measures of total airway resistance or flow do not reflect small areas of local inflammation within the nasal passages that can potentially disrupt transport to the olfactory epithelium. This latter conjecture is supported by the observation that inflammation present in specific nasal regions can differentially impact odor perception when odors are presented via the orthonasal versus the retronasal route. Data from the Monell-Jefferson Taste and Smell Clinic (Philadelphia, PA) suggest that retronasal olfaction might be more affected by sinus disease or polyposis than is orthonasal olfaction [19].

Several subsequent studies have supported the results of Cowart's study and provided additional characterization regarding the types and severity of rhinitis/rhinosinusitis that produce the greatest decrement in olfactory function. For example, Apter *et al.* [20] found that patients with chronic rhinitis, but no evidence of polyposis or rhinosinusitis, exhibited only moderate hyposmia on test battery of odor identification and detection, whereas rhinitic patients with polyps and/or chronic rhinosinusitis were more severely affected with anosmia.

Perhaps most significantly, the severity of olfactory impairment appears to vary according to whether the etiology of rhinitis/rhinosinusitis is allergic or nonallergic. With a self-administered survey given to more than 10,000 adults, Olsson *et al.* [8] estimated the prevalence of olfactory decrement to be significantly higher among patients with nonallergic rhinitis than among those with allergic rhinitis or among nonrhinitic individuals. Whereas, overall, the prevalence of hyposmia and the degree of impairment is greater among rhinitics than nonrhinitics, two recent studies using objective tests of olfactory function [7,21••,22] also revealed greater olfactory decrements among patients with nonallergic rhinitis than among those with seasonal or perennial allergic rhinitis.

Despite the paucity of studies that have objectively evaluated olfactory function among individuals with rhinitis/rhinosinusitis, in all studies to date, a subset of patients with established rhinitis (acute or chronic, allergic or nonallergic) exhibit impaired olfactory ability relative to controls. However, the prevalence and degree of impairment varies considerably with the type and severity of disease and age. Although olfactory dysfunction is not universally associated with polyposis [21••], patients with polyposis or a history of polypoid disease are more likely to suffer olfactory disability than those without [7,14,23•].

Mechanisms for Olfactory Loss in Rhinosinusitis

There are multiple potential mechanisms of rhinosinusitis-induced olfactory dysfunction, all of which relate to the physical and physiologic effects of inflammation. First, inflammation can impede transport of odorants to the sensory receptor cells due to airway constriction and altered mucus composition and transport (conductive). Second, inflammatory mediators released by infiltrating cells of the immune system can have direct or indirect effects on the structure or function of the neuroepithelium (sensorineural), including damage or inhibition to olfactory receptor neurons, fibrosis, and edema, which can impede or prevent successful regeneration of the neuroepithelium. Although conductive factors have often been considered to be the primary cause of olfactory impairment from rhinitis, the variability in degree of loss and recovery in the face of similar degrees of apparent airway restriction suggests that sensorineural factors might play a role as well.

Effects on nasal anatomy and airflow

Olfactory perception begins with the transport of volatile chemical molecules into the complex geometry of the nasal passages. Within the medical and scientific community, it has been widely held that impeded airflow to the olfactory cleft is the primary cause of olfactory loss in rhinitis. However, in nearly every study, neither direct measures of nasal airflow using anterior rhinometry nor congestion of the olfactory cleft have been shown to correlate with olfactory function. Studies of regional changes in nasal volume from CT scans provide support for the notion that congestion in certain regions will produce greater impact on olfactory function than that in other regions [24•,25]. Using a three-dimensional, anatomically correct model based on an individual patient's CT scan, Zhao *et al.* [26•] varied the nasal anatomy in two critical regions (the nasal valve and the olfactory cleft) and computed the change in local and global airflow. Although the total airflow through the nostrils did not change, the amount of airflow in the olfactory region varied by more than 700%, with only small changes in nasal anatomy. Therefore, it appears that even minor inflammatory changes can have effects on the ability of odorant molecules to access the olfactory epithelium that cannot be predicted from measures of total airflow, such as rhinometry and rhinomanometry.

Odorant deposition

The second stage of odor perception involves the diffusion of volatile chemicals through the mucus barrier to interact with receptor proteins residing on the olfactory receptor neuron (ORN) cilia. The physicochemical characteristics of the odorants and the rate at which they move across the mucus sheet are critical determinants of their ability to reach and penetrate to the appropriate receptor cells [27]. Mucus depth, quantity, and viscosity changes might also influence the solubility and diffusivity of odorant molecules and their clearance from the perireceptor environment. In both normal and pathophysiologic cases, viscosity and elasticity are the most important physical properties of mucus, enabling it to be transported by movement of the cilia [28]. Alterations in mucus viscosity (either increases or decreases) can affect the diffusion rate

of an odorant to and from the receptor site as well as diminish the efficiency with which energy is transferred from the beating cilia to the mucus blanket [29]. Alterations in the ciliary motility can similarly impair the diffusion and clearance of odorants to and from the receptor sites. Both mucus viscosity and ciliary function can be affected by various rhinopathic conditions. Across different studies and using different measurement techniques, rhinitis and rhinosinusitis patients have been shown to have significantly impaired clearance rates relative to healthy controls (average: 2.77 mm/min and 1.82 mm/min vs 4.27 mm/min, respectively) [30–32].

Effects on neuroepithelial structure

A third mechanism for olfactory impairment in rhinitis is inflammatory changes to the neuroepithelial integrity. Olfactory losses that fail to recover with treatment in the absence of congestion or inflammation might be due to structural changes in the sensory epithelium that have impaired its regenerative capacity. The human olfactory epithelium is a layered structure, comprising neuronal and non-neuronal cell types, that resides within the olfactory cleft and extends to varying degrees onto the superior turbinate and superior aspect of the medial turbinate [33]. Cilia found on the dendritic knob of ORNs extend into the mucus layer and are the site of receptor proteins involved in odorant binding [34]. In the healthy epithelium, olfactory receptor neurons regenerate continuously throughout the lifespan, presumably because of the inherently damaging impact of exposure to numerous pollutants and viruses. This regenerative process has been considered to be essential for preserving normal olfactory function throughout life [35].

Not surprisingly, however, a variety of pathologic changes have been observed in neuroepithelial biopsies from patients with chronic rhinitis. In a study of nonallergic rhinitis patients with and without olfactory deficits, the olfactory epithelium of those with olfactory losses was found to exhibit moderate or severe inflammatory changes [36••], whereas none of those with normal olfaction had severe pathology, and only 40% of those revealed moderate inflammatory changes. The olfactory epithelium was particularly degenerated over areas within the lamina propia exhibiting severe inflammation, thus documenting the extent to which nonallergic rhinitis can adversely impact the sensory epithelium and, thereby, disrupt olfaction. Several other studies have reported altered or degenerating olfactory epithelium in biopsies of patients with olfactory loss due to chronic sinusitis, viral infection or head trauma [37–39], or allergic rhinitis [40], including loss of the basement membrane and reduced thickness of the epithelium.

Keratinization of the epithelium is another response of epithelia to chronic inflammation and expression of specific keratin patterns that, although protective, might actually impair recovery of sensory epithelium after injury. Evidence in support of this idea comes from studies showing that keratin-expressing cells are increased in the olfactory epithelium of patients with chronic rhinosinusitis [37], and following toxic exposures [41]. Taken together, the anatomical and psychophysical data suggest that the inflammatory process might initiate destructive effects on the sensory epithelium that might overwhelm its ability to regenerate and repair.

Effects on signal transduction

Sensorineural changes might also result from direct or indirect effects of inflammatory mediators on receptor-cell function. Odor signals are generated through a complex biochemical signal transduction cascade that is triggered by the binding of odorant molecules to receptors in the membranes of olfactory cells [42]. Signal transduction involves odorants binding to receptor molecules that are linked to seven-membrane, G-coupled proteins (Golf) that activate adenylyl cyclase (AC III) and lead to the formation of cyclic AMP (cAMP), which directly activates cyclic nucleotide-gated channels. The release of cytokines from an inflammatory process can directly or indirectly influence this pathway and potentially interfere with neuronal development or the function of the mature olfactory receptor neurons.

Rhinosinusitis Therapies and Their Impact on Olfactory Recovery

Current treatment options for rhinosinusitis include treating the underlying disease, such as infection or allergy, administration of intranasal and/or systemic anti-inflammatory medication, and surgery. Pharmacotherapy for rhinitis and/or rhinosinusitis includes antibiotics, corticosteroids, antihistamines, and decongestants. Often, these treatments are administered in tandem to eliminate or treat infection and inflammation while relieving symptoms. By far, treatment with intranasal or systemic synthetic glucocorticoids is the most commonly used therapeutic intervention for rhinosinusitis and has been shown to be efficacious in the reduction of mucosal swelling and tissue eosinophilia [43]. Surgery is typically a last resort and is performed either when the patient presents with conditions for which surgery is considered necessary (polyposis), or when the condition is refractory to other treatment options [43].

Although treating rhinitis/rhinosinusitis with pharmacotherapy improves rhinitis symptoms, it often fails to result in significant or long-lasting improvement in olfactory function. The reasons underlying this variation in response are not clear. Several studies have assessed the impact of nasal and/or systemic glucocorticoids on olfactory performance in patients with chronic rhinitis/rhinosinusitis [44–47]. In an open-label prospective study, 39 patients with chronic rhinosinusitis and anosmia or severe hyposmia were treated with intranasal corticosteroid administered in the head-down (Mott) position for at least 8 weeks [45]. Although

rhinosinusitis symptoms were significantly improved following treatment, 41% of patients failed to exhibit any improvement in olfactory performance. Of those who responded to therapy, many had exhibited increases in olfactory sensitivity following previous corticosteroid therapy and spontaneous fluctuations in olfactory sensitivity. In a study of atopic rhinitis patients treated with a variety of regimens, less than 30% showed improvement in olfactory function [48]. Although systemic steroids appear to be more effective than nasally inhaled steroids in treating olfactory loss, significant numbers of patients fail to respond to oral steroid therapy, and the potential for adverse effects from long-term oral steroids has called the effectiveness of this treatment option into question [5]. To summarize, the data reviewed suggest that steroid therapy improves the pathology and symptoms of rhinitis more than the concomitant olfactory dysfunction. If this is true, steroid-insensitive mechanisms are responsible for much of the olfactory loss in rhinitis/rhinosinusitis.

Surgical treatment of rhinosinusitis among patients also experiencing some degree of olfactory loss has led to some degree of improvement in olfactory performance, but not all experience recovery of normal olfaction [21••]. Disease severity also plays a role in the degree of improvement that is observed. In a pre- and postsurgical study of chronic rhinosinusitis patients, individuals with the most severe disease classification and/or polyposis were the least likely to show improvement on an olfactory identification task. Postsurgical, adjunctive, intranasal steroid therapy has not been shown to improve recovery of olfactory function. These results provide further evidence that factors in addition to conductive ones might account for the olfactory dysfunction that is secondary to rhinitis and/or rhinosinusitis.

Conclusions

Olfactory disorders afflict a substantial number of individuals, can produce serious consequences for the detection of many olfactory warning signals (*eg*, smoke, spoiled food, and gas leaks) [1], and can have a significant impact on nutritional status, eating satisfaction, and many other issues related to quality of life [2]. Although, in general, all forms of rhinitis/rhinosinusitis result in a higher prevalence of diminished, distorted, or absent olfactory ability, patients with nonallergic rhinitis/rhinosinusitis and concomitant polyposis experience the highest rates and most severe degree of olfactory loss or distortion. The underlying mechanisms by which rhinitis/rhinosinusitis impact olfactory ability are likely to be multifactorial and might include some or all of the following: altered air flow and odor deposition; changes in mucus composition or effects of inflammatory mediators on receptor cell differentiation, maturation, or function.

Although pharmacotherapy and surgery can mitigate much of the pathology and symptoms of rhinitis/rhinosinusitis, the olfactory loss that can accompany this disorder is, in a substantial number of patients, partially or wholly refractory to current treatment options. However, the olfactory impairment associated with allergic rhinitis/rhinosinusitis has proven to be more reversible with appropriate therapeutic interventions (*eg*, intranasal synthetic glucocorticoids) than that associated with nonallergic rhinosinusitis.

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