International Consensus Statement in Allergy and Rhinology: Olfaction

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Abstract

Background: The literature regarding clinical olfaction, olfactory loss and olfactory dysfunction has expanded rapidly over the last two decades, with an exponential rise in the last year. There is substantial variability in the quality of this literature and a need to consolidate and critically review the evidence. It is with that aim that we have gathered experts from around the world to produce this International Consensus of Allergy and Rhinology: Olfaction.

Methods: Using previously described methodology, specific topics were developed relating to olfaction. Each topic was assigned a literature review, evidence-based review (EBR), or evidence-based review with recommendations (EBRR) format as dictated by available evidence and scope within the ICAR:O document. Following iterative reviews of each topic, the ICAR:O document was integrated and reviewed by all authors for final consensus.

Results: The ICAR:O document reviews close to 100 separate topics within the realm of olfaction, including diagnosis, epidemiology, disease burden, diagnosis, testing, etiology, treatment and associated pathologies.

Conclusion: This critical review of the existing clinical olfaction literature provides much needed insight and clarity into the evaluation, diagnosis and treatment of patients with olfactory dysfunction, while also clearly delineating gaps in our knowledge and evidence base that we should investigate further.

I. Introduction

The field of olfaction is a relatively young one. Detailed knowledge of the mechanisms of the olfactory system were only discovered in the second half of the twenty first century, with Richard Axel and Linda Buck awarded the 2004 Nobel prize for their landmark description of odorant receptors and the organization of the olfactory epithelium, bulb and cortex.[1] An explosion of investigation followed in both the basic science research realm as well as clinical study, steadily growing in number of publications as well as complexity of study design over the two decades that have followed, peaking within the last year as the COVID-19 pandemic brought loss of smell and taste to the forefront of international importance and recognition.[2,3]

In all the many decades prior to Axel and Buck's publication, publications listed in PubMed under "olfaction" totaled less than 5000. In the decade that followed, publications matched this number and over the next decade continued to accelerate until in the decade between 2011 and 2021, there were 13,618 publications, with 2,325 publications in the year 2020 alone.

Although basic science research is integral to our understanding of the system and invaluable in creating the foundation for any translational or clinical study, with the vast amount of literature to evaluate, we decided to limit this document to the existing clinical knowledge in the field of olfaction. Similar to other International Consensus in Allergy and Rhinology (ICAR) documents, on chronic rhinosinusitis (CRS) and allergic rhinitis (AR),[4,5,6] our goal with producing this manuscript is to summarize the best external evidence to provide practitioners the means to practice evidence-based medicine (EBM) when diagnosing and treating these patients. As is the case across many fields of medicine, especially those that affect patients less commonly, the quality of the existing clinical literature published on olfactory loss and dysfunction is highly variable, with studies ranging from well-designed randomized controlled clinical trials to summaries of expert opinion and conjecture. The goal of this International Consensus of Allergy and Rhinology: Olfaction (ICAR:O) was to critically review the literature for olfaction related epidemiology, psychological and social burden, pathophysiology, evaluation and diagnosis, and management.

With the management of olfactory loss or dysfunction being inherently a multi-disciplinary field, we endeavored to include authors from a wide array of expertise to ensure the highest and most insightful coverage of the subject. Over 50 international authors undertook a structured review of the literature in close to 100 topic areas related to olfaction. Although highly dependent on the quality of the existing literature, wherever possible recommendations based on the evidence were made, with benefit, harm and cost considerations reported. However, as noted in prior ICAR documents, this document is not a clinical practice guideline (CPG) and not a meta-analysis. In fact, due to the wide heterogeneity of the data and reporting measures found in the literature in this field, a meta-analysis would not be appropriate or possible. Many of our current treatment paradigms are based on relatively weak external evidence, illustrated well by the wide variation in treatment methodology that exists around the globe for these patients. When we do not have high level evidence to base our practice decisions on, it is in our best interest as clinicians and scientists to identify the gaps in our current knowledge and attempt to design and carry out studies that can help fill those gaps and therefore better help our patients.

As stated in all prior ICAR documents, this document should not be considered as determining standard of care or medical necessity and cannot be thought of as dictating care for any individual patient. Each patient has their own unique history, background, demographic and clinical circumstances which may affect the evaluation and treatment of their specific olfactory loss or dysfunction. Finally, the entire idea of creating a document such as this, that strives to gather and review all the existing clinical evidence on olfactory loss and dysfunction, is that by identifying the areas that need more research, more research will then be performed, and thus the evidence and recommendations made herein will change over time, and revisions will be made to them appropriately.

II. Methods

II.A Topic Development

All ICAR documents, including this one, follow the formula of literature review described in Rudmik and Smith in 2011, utilizing their method of iterative evidence-based review with

recommendations (EBRR).[7] Literature was analyzed, assessed for level of evidence and, when appropriate, recommendations were given.

The subject matter of clinical olfaction was divided into 75 topics. Each topic area was assigned a senior author, recognized as an expert in the field. Authors were selected based on prior authorship of significant contributions to the olfactory literature, and were selected from the fields of rhinology, neurology, and chemosensory science. Depending on the type of topic and the quality of evidence available in each topic, the section author was assigned either a simple literature review (LR), an evidence-based review (EBR), or an evidence-based review with recommendations (EBRR).

To provide the content for each topic, a systematic review of the literature for each topic using Ovid MEDLINE (1947 to July 2020), EMBASE (1974 to July 2020), and Cochrane Review databases was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standardized guidelines. The search began by identifying any previously published systematic reviews or guidelines pertaining to the assigned topic. Because clinical recommendations are best supported by randomized controlled trials (RCTs), the search focused on identifying these studies to provide the strongest level of evidence (LOE). When these did not exist, observational studies were then identified. Reference lists of all identified studies were examined to ensure all relevant studies were captured. If the authors felt as though a non-English study should be included in the review, the paper was appropriately translated to minimize the risk of missing important data during the development of recommendations.[8] One major exception to the search window was made for the section on COVID-19 related olfactory dysfunction. The evidence for this topic was rapidly evolving during the time of writing and editing of this manuscript, and we felt it would do the readership a disservice if we left out pertinent information that was only realized after the literature search window had closed.

To optimize transparency of the evidence, all included studies in EBR and EBRR topic sections are presented in a standardized table format and the quality of each study was evaluated to receive a level based on the Oxford LOE (level 1a to 5) (see **Table II.A-1**).[9] At the completion of the systematic review and research quality evaluation for each clinical topic, an

aggregate grade of evidence was produced for the topic based on the guidelines from American Academy of Pediatrics Steering Committee on Quality Improvement and Managements (AAP SCQIM)[10](see **Table II.A-2**). After providing an aggregate grade of evidence for each EBRR topic (A to D), a recommendation using the AAP SCQIM guidelines was produced (**Table II.A-3**). The recommendation was based upon the aggregate grade of evidence as well as the balance of benefit, harm, and costs. A summary of the EBRR development process is provided in **Figure II.A-1**.

IIB. Iterative Review

Each topic was written with appropriate tables and potential recommendations by the initial author assigned. Each section then underwent an online iterative review process using 2 independent reviewers (**Figure II.A-2**). Each iterative reviewer evaluated the completeness of the identified literature and evaluated whether EBRR recommendations were appropriate. If any content changes were suggested by the first iterative reviewer, these were sent back to the initial author to revise the section until all changes were agreed upon by the initial author and this first reviewer. The revised topic was then subsequently reviewed by a second reviewer. Both initial and first and second iterative authors of the topic agreed upon all changes before each section was allowed to proceed into the final ICAR statement stage.

Table II.A.1. Levels of evidence

Level	Diagnosis	Therapy/Prevention/Etiology
1	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Systematic review of randomized trials or *n*-of-1 trials
2	Individual cross sectional studies with consistently applied reference standard and blinding	Randomized trial or observational study with dramatic effect
3	Cohort study or control arm of randomized trial*	Non-randomized controlled cohort/follow-up study**
4	Case-series or case control studies, or poor quality prognostic cohort study**	Case-series, case-control studies, or historically controlled studies**
5	Not applicable	Mechanism-based reasoning

* Level may be graded down on the basis of study design, inconsistency between studies, indirectness of evidence, imprecision, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size or if a significant dose-response relationship is demonstrated.
** As always, a systematic review is generally better than an individual study.

Table II.A.2. Aggregate grade of evidence

Grade	Research Quality
A	Well-designed RCTs
B	RCTs with minor limitations Overwhelming consistent evidence from observational studies
C	Observational studies (case control and cohort design)
D	Expert opinion Case reports Reasoning from first principles

For topics with more limited evidence, the EBR process was completed with the evidence table. For those topics with sufficient evidence to produce a recommendation (*i.e.*, an EBRR), a recommendation using the AAP guidelines was produced. It is important to note that each evidence-based recommendation took into account the aggregate grade of evidence along with the *balance of benefit, harm, and costs* (**Table II.A-3**).

Table II.A.3. AAP defined strategy for recommendation development

<table>
<tr><th>Evidence Quality</th><th>Preponderance of Benefit over Harm</th><th>Balance of Benefit and Harm</th><th>Preponderance of Harm over Benefit</th></tr>
<tr><td>A. Well-designed RCT's</td><td>Strong Recommendation</td><td rowspan="3">Option</td><td rowspan="2">Strong Recommendation Against</td></tr>
<tr><td>B. RCT's with minor limitations; Overwhelmingly consistent evidence from observational studies</td><td rowspan="2">Recommendation</td></tr>
<tr><td>C. Observational studies (case control and cohort design)</td><td rowspan="2">Recommendation Against</td></tr>
<tr><td>D. Expert opinion, Case reports, Reasoning from first principles</td><td>Option</td><td>No Recommendation</td></tr>
</table>

Figure II.A-1

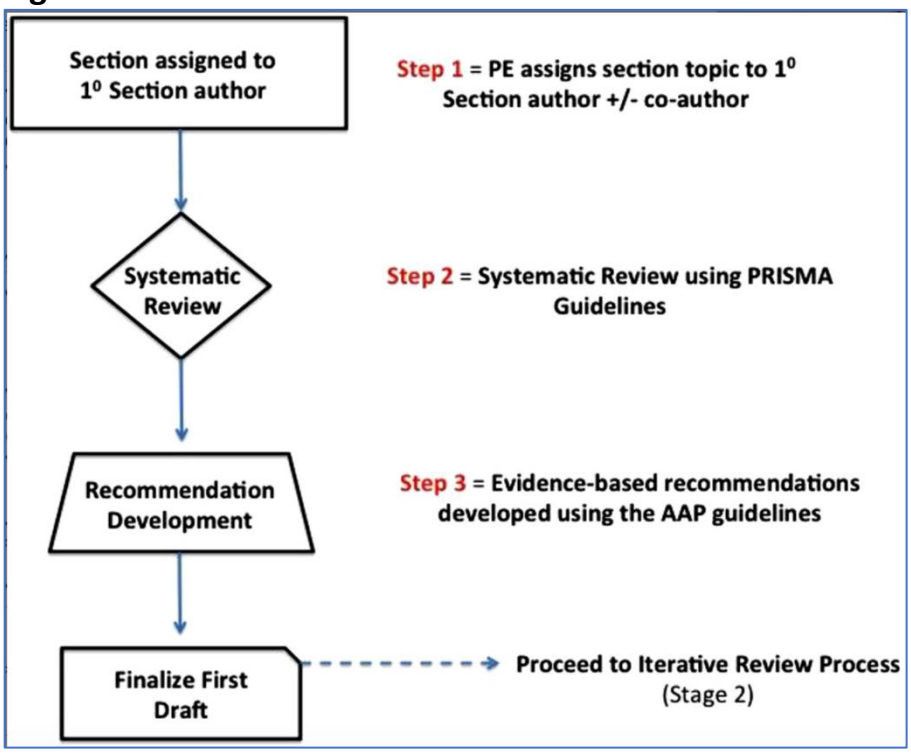
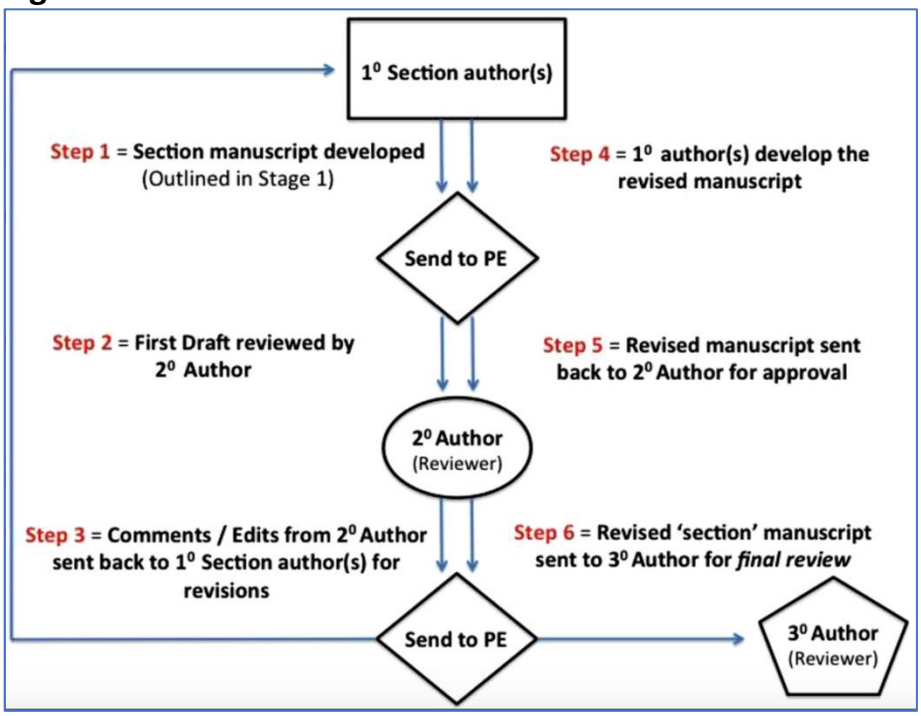


Figure II.A-2



IIC. ICAR:O Statement

After the review and completion of all topic sections, the principal editor (ZMP) compiled them into one ICAR:O statement. This draft document was then reviewed by all contributing authors who submitted suggestions and edits. Once consensus among all authors had been reached regarding the literature and final recommendations, the final ICAR:O manuscript was produced.

SECTION: III. Definitions

A. Anosmia and Hyposmia

Anosmia is defined as an absence of olfaction with an inability to detect and correctly identify odors, as measured by a validated, standardized olfactory test.[1-3] While anosmia, by definition, describes complete smell loss, functional anosmia refers to the possible existence of trace olfactory function but at a level not considered to be useful or noticeable in daily life.[2,4] Hyposmia or microsmia is defined as partial smell loss.[2,4] Specific anosmia is an inability to detect one or more specific odorants while olfaction of other odorants is intact.[5]

As self-assessment of olfactory loss can be unreliable, the diagnosis of anosmia is traditionally confirmed based on the absolute number of correct answers on psychophysical olfactory testing; with the threshold established from subjects with complete loss of smell.[2,3,6] Normosmia, normal olfactory function, for most olfactory tests is based on normative data from healthy 16-35-year-old subjects, although normative data has been collected for all age groups on certain tests, such as the University of Pennsylvania Smell Identification test (UPSIT).[3] Hyposmia is an absolute score below the 10th percentile of that normosmic group.[2,6,7] Hyposmia can be further delineated into mild, moderate or severe hyposmia.[3] Olfactory function should be assessed by validated tests of odor threshold and either odor identification or discrimination. Composite scores may be more reliable than tests of only one component of olfactory ability.[4]

B. Parosmia

Parosmia is defined as a qualitative dysfunction from a distorted perception of smell in the presence of an odor object.[1] These distorted smells are frequently reported to be disgusting or disagreeable and only very rarely would be considered pleasant. Common descriptors include “burned,” “foul,” “disgusting,” and “fecal.”[2–6] Patients often report difficulty in characterizing these odors, and therefore, these terms should be considered as shorthand for their unpleasantness, rather than definitively accurate descriptions. Parosmic experiences can range from “strange” to powerful feelings inducing nausea and the inability to eat

C. Phantosmia

Phantosmia is defined as a qualitative dysfunction of smell in the absence of an odor object. [1] Here, perception of an odor occurs without an external stimulus. Descriptors for phantom odors may be similar in some ways to those used for parosmia: “burned”, “chemical”, and “like cigarette smoke.”[2–5] It is often difficult for the subject to accept that there is no external source for these perceptions, and they often search their homes or work environments exhaustively, seeking the source. Unlike the qualitative changes experienced with parosmia, phantosmic perceptions can occur at any time. Sometimes, both parosmia and phantosmia can occur together, in the same patient.[4,5]

IV. The Individual Burden of Olfactory Dysfunction

A. Psychological Sequelae: Potential effects on interpersonal relationships and emotional state

The sense of smell serves three core purposes: prevention of close encounters with environmental hazards, monitoring and guidance of nutrition, and mediation of interpersonal communication.[1] Olfactory dysfunction hence disturbs functioning of all those domains. As a consequence, a substantial number of affected people state they experience a poorer overall quality of life,[2] which particularly affects emotional well-being and interpersonal relationships. Evidence of the costs of smell impairment will be summarized below with regard to both aspects. (Table

Emotional state

Previous research has repeatedly demonstrated associations between decreased olfaction and anhedonia, or depression.[3–5] Due to largely shared neural pathways (e.g., amygdala, hippocampus, insula, and orbitofrontal cortex),[6] this link is not surprising. Croy and Hummel[3] suggest possible mechanisms behind this association might include that i) dysfunction of the olfactory bulb (as the initial station of olfactory processing) results in decreased neural signaling into subsequent cortices; or ii) that the consequence of depressive behavior (e.g., withdrawal) leads to diminished olfactory input and consecutive diminished olfactory functioning. Regardless of the mechanisms involved, negative feelings such as anhedonia, sadness, fear or frustration are reported by about one third of patients suffering from olfactory loss,[2,7,8] with varying prevalence due to individual patient characteristics. For example, higher prevalence has been reported for hyposmic vs. anosmic patients,[9] while evidence regarding gender effects is mixed[9,10] but with women reporting particular suffering in social domains.[8] The latter may be explained by the generally higher value placed on the sense of smell and importance of olfaction in women, in particular young women, compared to other demographic groups.[11] Individuals with reduced self-esteem have been shown to be prone to the emergence of depressive symptoms from olfactory losses.[12] Single reports disclose disturbances in a wide array of life areas, including hygiene behavior, domestic life[8] or in the enjoyment of simple pleasures, such as the smell of flowers, perfumes, or nature.[13] In view of these reports, the low general quality of life measured in these populations is not surprising. However, not every patient with an olfactory disorder is bothered to a substantial degree. It has to be considered that most reported data is obtained from patients seeking help, thus suggesting selection bias.[2,14] In contrast, Oleszkiewicz et al[15] revealed that people with unnoticed olfactory loss do not differ from controls in terms of their well-being. However, within the group of patients disturbed by their sensory loss, concomitant psychological burden should be carefully assessed and diagnosed. Practitioners should be especially aware of the demographic groups most affected[16]. For such predisposed populations, suitable interventions, e.g. consultation with a psychologist or psychiatrist, should be provided in order to prevent manifestation and exacerbation of long-term side effects such as social isolation or anxiety.

Interpersonal relationships

Human chemosensory signals, such as those released from body odor, convey various data points of information about the individual, which inform sensory social communication. This information reflects hormonal[17] or emotional states,[18–20] personality traits,[21] as well as the genetic constitution[22] of the releaser. Familiar body odors can signal comfort,[23,24] and may be associated with affectionate feelings.[25,26] Olfactory dysfunction is thus likely to be associated with deficits in receiving, processing and interpretation of such interpersonal sensory information. Patients with olfactory disorders do frequently complain about impairment in social situations, isolation, or feelings of social insecurity.[2,13,27] This is of significant relevance in the context of intimate relationships, such as relationships between parent and child, or between romantic partners.[7,28] Regarding the former, parents report the body odor of their child as an affective and instrumental cue,[26] as infant odor is associated with neural correlates of reward in the maternal brain.[29,30] The latter was studied by Mahmut and Croy[31] who reported evidence for the involvement of olfaction in "initiation, maintenance and breakdown of romantic relationships". As body odors signal attractiveness[32,33] or mediate sexual experience[34] in normosmic individuals, dysosmic patients exhibit a reduced number of sexual partners and suffer from enhanced partnership insecurity[35] as well as reduced sexual desire, which can affect intimacy and pleasure.[36] The reduced self-confidence in social domains may hamper both the quality of established relationships and also the development of new relationships, thus increasing risk of social isolation,[37.38] which, in turn, might be a predictor for depressive symptoms. However, once again this relation has only been found for individuals troubled enough by their olfactory impairment to seek professional help, and not by people who are unaware and unaffected by their deficit.[15]

Table IV.1. Section Evidence Summary Table: Emotional State

Study	Year	Level of Evidence (1 to 5)	Design	Population	Outcome	Conclusion
Stevenson[1]	2010	4	Literature review	Animal studies, olfactory loss	Identification and categorization of the main functions of human olfaction	Identification of three major classes of functions:

				patients, human studies on evidence of that function		Ingestion, avoiding environmental hazards, social communication with specific sub-functions
Croy, Nordin, and Hummel[2]	2014	4	Literature review	Quantitative, qualitative and congenital olfactory disorder patients	Links between olfactory impairment and general quality of life/depression	Olfactory impairment associated with disturbances in various life areas (food, harmful event detection, social situations); majority of olfactory disorder patients deals well but a limited proportion suffer from reduced quality of life and increased depression scores
Croy and Hummel[3]	2017	4	Literature review	Healthy individuals, depressed patients, olfactory disorder patients	Links between olfaction and depression	Interaction between olfaction and depression by two suggested pathways 1) impaired olfactory function as a consequence of reduced olfactory attention and input 2) OB as a marker for enhanced vulnerability to depression
Kohli et al[4]	2016	4	Literature review	Primary depression patients or primary olfactory dysfunction patients	Links between olfactory dysfunction and depression	Reciprocal relationship: Depressive patients show reduced olfactory performance, olfactory dysfunction patients exhibit depressive symptoms
Schablitzky and Pause[5]	2014	4	Literature review	Healthy individuals, distinct groups of Major depressive disorder (MDD),	Olfactory performance (odor sensitivity, identification, discrimination, and odor ratings) in depressed patients and in healthy individuals experiencing only some depressive symptoms or a transient state of sad	MDD relates to reduced olfactory sensitivity, but not to odor identification / discrimination, no associations in BPD/SAD but in healthy individuals

				bipolar disorders (BPD), seasonal affective disorder (SAD)	mood	exhibiting subclinical depressive states
Rochet et al[6]	2018	4	Literature review	Healthy individuals, depressed and clinically improved patients, olfactory disorder patients	Links between olfaction and depression; olfactory markers of depression	Olfactory impairment affects quality of life / daily life, associations with depression; (heterogenous findings regarding olfactory markers of depression; Reciprocal relationship between olfactory dysfunction, depression / quality of life
Erskine and Philpott[7]	2019	4	Case-series, qualitative research design	Smell disorder patients	Subjective experiences of smell disorder patients	Identified themes: negative emotional impact, feelings of isolation, impaired relationships and daily functioning, impact on physical health and the difficulty and financial burden of seeking help
Philpott and Boak[8]	2014	3	Cohort study	Olfactory disorder patients	Consequences of smell disorder on patients´ daily life and affected areas	Olfactory dysfunction associated with psychological impairment and reduced life quality: 43% of the patients report depression, 45% report anxiety, 92 % impairment of eating, 57% isolation and 54% relationship difficulties; women more affected then men
Frasnelli and Hummel[9]	2005	2	Cross-sectional controlled study	Olfactory disorder (quantitative and qualitative) patients and healthy controls	Qualitative and quantitative olfactory dysfunction and impact on daily life	Patients with parosmia as well as quantitative olfactory dysfunction show higher rates of daily life complaints when compared to patients suffering from

						quantitative olfactory impairment only; quantitative olfactory impairment patients exhibited more complaints than healthy controls
Desiato et al[10]	2020	1	Systematic review and meta-analysis	Study cohorts recruited from general population	Prevalence of olfactory dysfunction in the healthy general population	Overall prevalence of olfactory dysfunction of 22.2%, reported prevalences are higher when measured with expanded identification tests < 8 items, and in subjects > 55 yrs
Murr et al[11]	2018	2	Prospective controlled study	Olfactory disorder patients and healthy controls	Importance of olfaction	Highest importance of olfaction in young, healthy women (≤25 yrs). Olfactory disorder patients reported decreased importance of olfaction; possible coping mechanism.
Kollndorfer et al[12]	2017	2	Prospective controlled study	Anosmic patients and healthy controls	Link between self-esteem and quality of life in olfactory dysfunction	Decreased life quality and reduced body-related self-esteem in anosmic patients; low life quality and self-esteem related to depressive symptoms
Keller and Malaspina[13]	2013	4	Patient report series	Patients with olfactory dysfunction	Subjective experiences with olfactory loss	Impaired life quality, in particular reflected by reported social isolation and anhedonia
Blomqvist et al[14]	2004	3	Cohort study	Patients with olfactory dysfunction	Well-being and coping in patients with olfactory loss	Impaired life quality (e.g., physical health, financial security, social relations, leisure, emotional stability) and negative effects on well-being; patients use problem- and emotion-focused coping
Oleszkiewicz et al[15]	2020	2	Cohort study	Individuals declaring normal sense	Undetected olfactory loss and relationship to cognitive performance and well-being	59 of 203 individuals with impaired olfaction; differences

				of smell		between affected and non-affected subjects in cognitive functioning but not in well-being and chemosensory communication
Schäfer, Schriever, and Croy[16]	2021	4	Literature review	Olfactory disorder patients, healthy individuals	Causes and consequences related to the main functions of olfaction	Impaired enjoyment of food, worries about hazards and social insecurities lead to decreased life quality; recommendation to focus medical and psychological treatment options on patients suffering from concomitant impairment due to smell loss, provide treatment and coping strategies

Table IV.2. Section Evidence Summary Table: Interpersonal Relationships

Study	Year	Level of Evidence (1 to 5)	Design	Population	Outcome	Conclusion
Lobmaier et al[17]	2018	2	Cross-sectional experimental study	Healthy individuals, men rating female body odor samples	Relation between body odor attractiveness and reproductive hormones	Men agreed on body odor attractiveness ratings, which were higher in women with higher estradiol and progesterone levels
de Groot et al[18]	2015	2	Cross-sectional experimental study	Healthy individuals	Relation between chemosignals (body odors sampled in a happy emotional state) and emotional reaction of the receiver	Exposure to body odor collected from senders of chemosignals in a happy state induced a facial expression and perceptual-processing style indicative of happiness in the receivers
Gelstein et al[19]	2011	2	Cross-sectional experimental study	Healthy individuals, men sniffing women´s tears	Relation between chemosignals (women´s tears) and emotional reaction of the receiver	Sniffing of tears related to reduced sexual appeal evaluation of women´s faces, reduced self-related arousal, reduced testosterone levels as well as reduced brain

						activity related to sexual arousal
Prehn-Kristensen et al[20]	2009	2	Cross-sectional experimental study	Healthy individuals	Neural reactions in response to perception of chemosignals (body odors sampled in anxiety vs. sport state)	Anxiety body odors activate brain areas related to processing of social emotional stimuli (fusiform gyrus), and regulation of empathy (insula, precuneus, cingulate cortex)
Sorokowska, Sorokowski, and Szmajke[21]	2012	2	Cross-sectional experimental study	Healthy individuals	Link between body odor, personality traits and dominance	Correlation between self-rated odor donor personality traits and external judgments based on odor alone for extraversion, neuroticism and dominance
Wedekind et al[22]	1995	2	Cross-sectional experimental study	Healthy individuals, women rating male body odors	Link between MHC, body odor and attractiveness	More pleasant perception of body odors when MHC dissimilar; preference erased in women taking oral contraception
Rattaz et al[23]	2005	2	Cross-sectional experimental study	Full-term newborns	Effectiveness of familiar and unfamiliar odors in soothing during routine heel-stick	Familiar odor (maternal milk/vanilla) associated with reduced stress response
Granqvist et al[24]	2019	2	Cross-sectional experimental study	Healthy individuals	Effect of exposure to partner´s body odor on discomfort and psychophysiological stress	Partner body odor decreased subjective discomfort during a stressful event; reduced skin conductance in highly secure subjects
Lundström and Jones-Gotman[25]	2009	2	Cross-sectional experimental study	Healthy individuals	Links between olfactory identification ability and degree of romantic love in partnership	Negative correlation between degree of romantic love and ability to identify body odor of an opposite-sex friend but not of their same-sex friend
Okamoto et al[26]	2016	3	Cohort study	Healthy individuals, parents	Links between child rearing and olfaction	Parents actively seek their child´s odor in daily rearing, child´s head most frequent source of affective experiences and child´s bottom of

						practical
Croy, Nordin, and Hummel[2]	2014	4	Literature review	Quantitative, qualitative and congenital olfactory disorder patients	Links between olfactory impairment and general quality of life/depression	Olfactory impairment associated with disturbances in various life areas (food, harmful event detection, social situations); majority of olfactory disorder patients deals well but a limited proportion suffer from reduced quality of life and increased depression scores
Drummond, Douglas, and Olver[27]	2013	4	Case series, Qualitative research design	Patients with severe traumatic brain injury and olfactory loss	Impact of olfactory impairment on daily activities and social participation	Olfactory dysfunction has a significant impact on various activities and social role
Keller and Malaspina[13]	2013	4	Patient report series	Patients with olfactory dysfunction	Subjective experiences with olfactory loss	Impaired life quality, in particular reflected by reported social isolation and anhedonia
Brämerson, Nordin, and Bende[27]	2007	3	Prospective cohort study	Olfactory disorder patients	Description of how quantitative and qualitative olfactory disorders are diagnosed, what the etiologies are, and how quality of life is compromised in patients	Patients with reduced sense of smell, often combined with qualitative disorders, exhibit significantly reduced quality of life, particularly in paid employment, household work, social and family life
Erskine and Philpott[7]	2019	4	Case-series, qualitative research design	Smell disorder patients	Subjective experiences of smell disorder patients	Identified themes: negative emotional impact, feelings of isolation, impaired relationships and daily functioning, impact on physical health and the difficulty and financial burden of seeking help
Lundström et al[29]	2013	2	Cross-sectional study	Healthy individuals, comparing mothers and nulliparae	Neural responses to unfamiliar infant body odors	Infant body odors elicit reward-related activations, maternal status-dependent activity in neostriatal

						areas
Schäfer, Michael, and Croy[30]	2019	2	Cross-sectional study	Healthy individuals, mothers	Neural responses to body odor of their own and unfamiliar infant	Infant body odors elicit regions of pleasure and reward independent from familiarity (own vs. unfamiliar baby)
Mahmut and Croy[31]	2019	4	Literature review	Healthy individuals, olfactory disorder patients	Links of olfactory ability and romantic relationships	Body odor perception moderates mate choice, provides a source of comfort in existing relationships and alteration of preference may signal the breakdown of a relationship
Herz and Inlicht[32]	2002	3	Cohort study	Healthy individuals	Importance of social and physical traits in heterosexual attraction	Women ranked body odor as more important for attraction than looks, natural body odor as the most influential olfactory variable for sexual interest in men and women, men rated good looks as most important
Sorokowska et al[33]	2018	2	Cross-sectional study	Healthy individuals	Body odor attractiveness and HLA similarity	Women not using hormonal contraception rated HLA similar body odors as less attractive, no influence of HLA similarity was observed for women using hormonal contraception and men
Bendas, Hummel, and Croy[34]	2018	2	Cross-sectional study	Healthy individuals	Link between odor threshold and sexual desire, sexual experience and sexual performance	High olfactory sensitivity relates to higher pleasantness of sexual activities, higher frequency of orgasms in women
Croy et al[35]	2012	2	Cross-sectional study	Congenital anosmic patients and healthy controls	Link between olfactory impairment and functions of daily life	Patients differed only slightly from controls, in terms of enhanced social insecurity, increased risk for depressive symptoms

						and household accidents
Schäfer et al[36]	2019	2	Cross-sectional study	Smell disorder patients and healthy individuals	Link between olfactory impairment and sexual desire	29% of patients reported decreased sexual desire after olfactory loss, predicted by depressive symptoms and olfactory function; no differences in standardized questionnaire
Oleszkiewicz et al[15]	2020	2	Cohort study	Individuals declaring normal sense of smell	Undetected olfactory loss and relationship to cognitive performance and well-being	59 of 203 individuals with impaired olfaction; differences between affected and non-affected subjects in cognitive functioning but not in well-being and chemosensory communication

- **Olfactory Dysfunction Effects Interpersonal Relationships and Emotional State**
  Aggregate Grade of Evidence: B (Level 1: one study, Level 2: 20 studies, Level 3: 5 studies, Level 4: 12 studies)

SECTION: IV. The Individual Burden of Olfactory Dysfunction

B. Safety

Chemosensation plays a critical role for all organisms, from single-celled amoebas to higher level organisms such as humans, to respond to their environments. In humans, while much attention is directed toward the impact of olfactory dysfunction on feeding behaviors and quality of life,[1–3] the critical importance of olfaction on personal safety – most notably the avoidance of injury from fires, ingestion of spoiled food, and inhalation of noxious chemicals, cannot be disregarded.[3] Objective data directly linking smell loss to such potential harms is lacking. An early study attempted to explore causes of the disproportionate number of deaths in persons over 60 years of age in England due to “coal-gas poisoning,” demonstrating that 33% of those over 65, compared with 7% under 65 years were unable to recognize the odor of

"town gas."[4] Another study reporting on the demographics of fire victims in New Jersey showed an overrepresentation of the very young and elderly among fire victims, when compared to state demographics, arguing this might be explained in part by reduced olfaction in the latter group.[5] Studies employing patient reports of having experienced olfactory dysfunction related safety events showed significant differences between anosmic, hyposmic, and normosmic populations for both acquired[6–8] and congenital[9] olfactory deficits. The odds ratio of experiencing "hazardous events" compared with controls was 2.94 for anosmics, and 1.30-2.18 for hyposmics of varying degrees, while increased risk was also noted in patients < 65 years of age and females, potentially related to differing risks of exposure during work and home activities.[8] However, difficulties exist in normalizing data for frequency of exposure to such events, as well as length or nature (quantitative vs. qualitative) of olfactory dysfunction. Many studies have explored the quality of life impact of olfactory dysfunction. Those including safety related issues have indicated increased incidence of fear or concern for gas leaks (49-60%[1,2,10,11]), smoke/fires (30-50%[2,11–14]), chemical exposures (6-40%[2,14]), and eating spoiled foods (15-71%[1,10–14]). However only two of these studies employed some form of olfactory-intact control population, with one relying on patient report of function,[2] and the other using objective testing.[1] Most authors advocate the importance of counseling olfactory impaired patients on these hazards and compensatory strategies for risk mitigation. The "Individual Importance of Olfaction Questionnaire" has been used to compare the importance of olfaction in daily life, showing lower scores in anosmics compared with hyposmics or controls,[15] suggesting compensation among afflicted individuals. However, research does not support cross-modality compensation among sensory impaired individuals. Thresholds for detection of rotten food odor showed no differences between blind or deaf subjects, or unimpaired controls.[16]

Limited primarily subjective data suggests an increased risk of personal safety events, as well as deficits in quality of life associated with fear of such events, in patients with impaired olfaction. Although appropriate intervention studies are lacking, most authors suggest counseling impaired patients on risk mitigation strategies as a low cost risk intervention.

- **Olfactory Dysfunction Affects Personal Safety**

Aggregate Grade of Evidence: C (Level 4: 14 studies, Level 5: 1 study)

SECTION: IV. The Individual Burden of Olfactory Dysfunction

C. Increased Mortality

Olfaction has been linked to a number of conditions, most notably to neurodegenerative disease and the ultimate health outcome: mortality. 10 relevant articles are included in this evidence based review. One of these articles was a re-analysis of data from previously published work, but was included here for completeness.

The first paper to connect impairment in odor identification (12-item University of Pennsylvania Smell Identification Test [UPSIT]) with increased, adjusted risk of death was published by Wilson et al[1] in 2011 in the Rush Memory and Aging Project, a prospective, longitudinal study of the development of Alzheimer's Disease. Consequently, Gopinath et al[2] examined this question in the Blue Mountains Eye Study in Australia. Although they found a relationship between the San Diego Odor Identification Test score and increased risk of all-cause mortality, the association was not significant after adjustment for cognition. Pinto et al[3] demonstrated a robust relationship between poor odor identification (5-item Sniffin' Sticks) and odds of mortality in the National Social Life, Health, and Aging Project, a nationally representative dataset. Using the full, 40-item UPSIT, Devanand et al[4] showed increased hazard of death for those in the lower quartiles of function compared to the highest in a multi-ethnic community cohort from New York City, using the Washington Heights/Inwood Columbia Aging Project. Schubert et al[5] examined data from the Epidemiology of Hearing Loss Study, a population-based longitudinal study of sensory function and aging in Beaver Dam, WI, and found sensory dysfunction predicted mortality but was specific to olfaction (8-item San Diego Odor Identification Test) and not hearing or vision. Ekström[6] expanded on these findings using data from the Betula project, a Swedish population-based longitudinal study of aging, memory, and health, and determined that the relationship between decreased odor identification (13-item Scandinavian Odor-Identification Test) was not mediated by conversion to dementia prior to death, suggesting that the mechanism was not solely via the development of neurodegenerative disease. Similarly examining underlying mechanisms, Leschak et al[7] found that social network size partially

mediated the olfactory-mortality link in women in a reanalysis of NSHAP data, implicating social context. Laudisio et al[8] found that olfactory dysfunction (self-reported inability to detect at least 2 of 3 common odors) was associated with reduced survival, an association which varied according to frailty and systemic inflammation (serum increased interleukin-6 levels) in a prospective population-based study of the development of late life disability in Tuscany, Italy, (the Invecchiare in Chianti" [InChianti] study). Recently, Liu et al[9] found a close connection between decreased odor identification (12-item UPSIT) and death in the Health, Aging, and Body Composition study, which examined older adults from Pittsburgh, Pennsylvania, and Memphis, Tennessee. Interestingly, they identified neurodegenerative and cardiovascular diseases as key outcomes and showed that neurodegenerative diseases explained only 22% and weight loss explained only 6% of the higher 10-year mortality among participants with poor olfaction. This study had the longest follow-up. Finally, Choi et al[10] linked 2013-2014 National Health and Nutritional Examination Survey participants to the National Death Index and found that objective olfactory impairment predicted 5 year mortality in those 65 year old and older but not in those in middle age in adjusted analyses.

These studies are all of sizable cohorts and include diverse older adult participants in a variety of populations across the world, with specific inclusion and exclusion criteria. All (excepting the InChianti study) objectively assess odor identification, although these rely on this modality over others (e.g., sensitivity or threshold or hedonics). We note that they do so in completely different ways using different forms of testing, both long and short. All control for key confounding factors and all include objective measures. The analysis strategy varies across the studies (logistic regression, cox analyses, hazard ratios, etc.). Nevertheless, almost all of these studies found robust (excepting the Blue Mountain study) and consistent relationships between poor olfaction and subsequent mortality (time to follow-up ranged from 4.1 – 13 years). Several provide dose response analyses. Thus, the aggregate level of evidence supporting a connection between olfaction and death is B (overwhelming consistent evidence from 9 observational studies, all level 2). These conclusions are viewed as extremely strong given the inability to perform randomized trials for this question.

Table. IV.3 Section Evidence Summary Table: Increased Mortality						
Study	**Year**	**Level of Evidence (1 to 5)**	**Design**	**Population**	**Outcome**	**Conclusion**
Wilson et al[1]	2011	2	Longitudinal Cohort Study	Retired Chicago area US adults, mean age 79.7	All-cause mortality; Mean 4.2 year	Difficulty with odor identification is associated with increased risk of death.
Gopinath et al[2]	2012	2	Longitudinal Cohort Study	Australian adults age≥ 60	All-cause mortality; 5 year	The relationship between olfaction and mortality may be largely mediated by cognitive impairment.
Pinto et al[3]	2014	2	Longitudinal Cohort Study	US adults age≥ 57	All-cause mortality; 5 year	Olfactory function is one of the strongest predictors of 5-year mortality in a nationally representative samples of older US adults.
Devanand et al[4]	2015	2	Longitudinal Cohort Study	New York City US adults, Medicare beneficiaries, age≥ 65	All-cause mortality; Mean 4.1 year	Anosmia is a particularly strong predictor of dementia.
Schubert et al[5]	2017	2	Longitudinal Cohort Study	Beaver Dam, WI US adults age 53-97 years	All-cause mortality; Mean 12.8 year	Olfactory impairment, but not hearing or visual impairment, is associated with increased mortality.
Ekström et al[6]	2017	2	Longitudinal Cohort Study	Swedish adults, age 40 - 90	All-cause mortality; 10 year	Presence or absence of dementia does not attenuate the association between olfactory loss and mortality.
Leschak and Eisenberger[7]	2018	2	Longitudinal Cohort Study	Older US adults ages≥ 57	All-cause mortality; 5 year	Social network size partially mediated the olfactory-mortality link in females (nationally representative samples of older US adults)
Laudisio et al[8]	2019	2	Longitudinal Cohort Study	Italian adults ages ≥65	All-cause mortality; 9 year	The relationship between olfaction and mortality may be mediated through frailty, possibly via inflammation.

Liu et al[9]	2019	2	Longitudinal Cohort Study	Pittsburgh, PA, and Memphis, TN, US adults, ages 70 to 79	All-cause and cause-specific mortality; 3, 5, 10, and 13 year	Neurodegenerative diseases and weight loss explain only part of the increased mortality.
Choi et al[10]	2021	2	Cohort study with National Death Index followup	US adults adult >40	All-cause mortality; 5 year	Objective (but not subjective) olfactory dysfunction is associated with increased mortality among older (≥65 years) but not middle-aged (40-64 years) US adults.

- **Decrease in Olfaction is Associated with Increased Mortality**

  Aggregate Grade of Evidence: B (Level 2: 10 studies)

SECTION: V. Anatomy and Physiology

A. Olfactory epithelium to olfactory bulb

The peripheral olfactory organ is the olfactory epithelium (OE), a true neuroepithelium that lines the olfactory cleft of the nasal cavity, including the ventral cribriform plate, the medial vertical lamellae of the superior turbinates as well as variable portions of the middle turbinates, and the superior portion of the nasal septum.[1-4] While the remainder of the nasal cavity and paranasal sinuses are lined by respiratory mucosa, the specialized olfactory neuroepithelium is composed of several distinct cell types: olfactory sensory neurons (OSNs), basal cells, sustentacular cells, microvillar cells, and ducts from Bowman's glands. Deep to the OE lies a lamina propria containing olfactory nerve fascicles with non-myelinating ensheathing glia, blood vessels, and Bowman's glands. Immune cell populations may be abundant within the olfactory mucosa. Inspired odors selectively activate OSNs, whose axons form cranial nerve I and project to the olfactory bulbs, terminating upon specific glomeruli.[5] Odor molecules reaching the olfactory cleft are detected by olfactory receptors (ORs), G-protein coupled receptors expressed on neuronal immotile cilia embedded in the mucus layer at the OE surface.[6,7] Odorant molecules use the mucus layer to bind to these receptors, and binding triggers OSN depolarization. The OR family in humans contains approximately 350 genes, and

evidence suggests that a given OSN generally expresses a single OR.[7,8] Distinct ORs are activated by specific sets of odors and may be broadly or narrowly tuned.[9] Each olfactory bulb glomerulus receives input from a subset of OSNs expressing the same OR proteins.[10] In this way, the pattern of glomerular activation in the olfactory bulb maps the neural response to different odorants.

An important feature of the OE is its reparative capacity. OSNs, exposed to the nasal airspace, are vulnerable to injury, and neuronal lifespan is variable and regulated by multiple factors.[11–13] Like other self-renewing epithelia, basal stem and progenitor cells in the OE divide and produce new cells as needed to maintain epithelial homeostasis under typical conditions.[14,15] In animal models, OE basal cells can produce OSNs, sustentacular cells, and microvillar cells.[16,17] Olfactory injury and repair has been well-studied in rodent models,[18–20] and evidence suggests similar repair mechanisms are active in adult humans.[8] Nonetheless, acquired olfactory disorders in humans remain incompletely understood and are therefore clinical challenges.

SECTION: V. Anatomy and Physiology

B. Olfactory bulb to olfactory cortical structures

The axonal projections from the sensory neurons of the olfactory epithelium (OE) are conveyed by the olfactory nerve (CN I) to the olfactory bulb (OB). The bulb is a laminated structure consisting, from superficial to deep, of 1) an outermost olfactory nerve layer; 2) a glomerular layer encompassing over a thousand pockets of neuropil, each termed a glomerulus, wherein olfactory axons synapse with the interneurons that surround the glomeruli and with the deeper relay neurons; 3) an external plexiform layer that contains one type of relay neuron, the tufted (T) cells, and several other interneuronal cell types; 4) the mitral (M) cell layer, the other type of projection neuron; 5) an internal plexiform layer with multiple additional interneuronal types; 6) an internal granular layer with its massive population of axonless granule cells that sharpen the patterns of M/T cell activity; and 7) a vestigial ependymal layer derived from the olfactory ventricle that serves as the migratory pathway for newly born periglomerular neurons and granule cells throughout life.[1] Projections from the M/T cells in the lateral olfactory tract sweep

over the surface of the three-layered paleocortex of the ventral forebrain before synapsing in cortical layer I.[2] Multiple distinct areas are innervated by the OB and are collectively categorized as the primary olfactory cortex (POC), including the anterior olfactory nucleus, olfactory tubercle, piriform cortex, cortical amygdala, and lateral entorhinal area. These cortical areas are extensively interconnected ipsilaterally and contralaterally with each other.[1] Smell information encoded by the POC is carried from the lateral entorhinal area to the hippocampus via the lateral perforant path, to deep portions of the amygdala and the lateral hypothalamus by the projection of the endopiriform nucleus deep to the POC, and to the orbitofrontal cortex (OFC) both directly and via the mediodorsal nucleus of the thalamus.[1]

The receptotopic organization of the projections from the OE to the OB converts odorant stimuli into a spatial map of activity across the glomerular layer of the OB, with different patterns produced by different odorants.[3] The spatial map of activity is sharpened by the circuitry of the bulb. The neural processing by the bulb is also modulated on the basis of sensory experience; parts of the OB that respond to odorants that are behaviorally associated with positive or negative reinforcement incorporate a larger number of newly born interneurons.[4] In contrast, the projection of the bulb onto the piriform cortex is spatially diffuse[2]; the axons of M/T cells receiving synaptic input from a single glomerulus disperse across the piriform cortex and the projections from functionally disparate glomeruli are largely indistinguishable from each other.[5] An exception is the projection to the cortical amygdala where the M/T cells of individual glomeruli also project broadly but innervate distinct patches that differ from one glomerulus to the next.[5] In terms of odorant representation in the piriform cortex, spiking activity is sparse and likewise distributed.[6,7] The olfactory tubercle apparently encodes odorant valency (whether a smell is considered pleasant or unpleasant) and is considered a part of the ventral striatum with a dense innervation by midbrain dopaminergic neurons.[8] At the higher cortical level, the OFC also seems to integrate odorant and reward information to help guide motivated behavior.[9]

SECTION: VI. Incidence and Prevalence

The absolute precise incidence and prevalence of olfactory disorders are actually still unknown. Despite increasing efforts to characterize and diagnose olfactory dysfunction and its numerous etiologies, prevalence rates range widely from approximately 1.5%-25% worldwide. The wide range of published epidemiologic data is largely secondary to heterogeneity in olfactory testing methodology and study populations. There is at least concordance that olfactory dysfunction increases in prevalence with age and is more common in males relative to females.[1,2]

The methods of olfactory assessment used in epidemiologic studies vary widely. Though a multitude of dedicated olfactory assessment tools are available worldwide, self-reported olfactory dysfunction is a commonly used metric.[2,3] While self-report measures are valuable, these assessments typically lack sensitivity and underestimate the degree of olfactory dysfunction as compared to psychophysical instruments.[4,5] Nonetheless, the lack of an accepted, universal psychophysical instrument, coupled with wide variation in patient demographics, exposures, and cultural differences across studies, makes determination of prevalence rates challenging.[1]

Self-reported prevalence rates have been explored in several large, population-based studies. A survey of approximately 80,000 United States (US) adults over 18 years of age, utilizing national adjustment estimates, extrapolated that 1.4% of the US adult population experienced olfactory impairment. This prevalence rate increased markedly in older individuals, with 40% of persons over the age of 65 reporting olfactory dysfunction.[6] Meanwhile, olfactory questionnaires from a nationally representative Korean database reported a prevalence rate of olfactory dysfunction of 4.5%.[7] Two additional studies in Europe and the US, using questionnaires aimed primarily at determining the prevalence of chronic rhinosinusitis, reported prevalence rates of olfactory dysfunction in 7.6% and 9.4%, respectively.[8,9]

Between 2011-2014, the US nationally representative NHANES database queried participants regarding the presence and frequency of olfactory disturbances., The estimated prevalence of olfactory disturbances was 10.6% ± 1.0% when patients were asked if they experienced a smell disturbance in the preceding 12 months; however, when considering participants with self-reported changes in olfactory function “since age 25” prevalence rates increased to approximately 23%.[10,11] Meanwhile, psychophysical assessment utilizing the

Pocket Smell Test demonstrated rates of 12.4% and 13.5% from the 2011-2012 and 2013-2014 interview cycles, respectively.[12,13] In the same database, 6.5% of participants experienced phantom odor perception.[14]

Several additional large population-based studies have included psychophysical measures of olfactory function. Utilizing the Scandinavian Odor-Identification Test in a nationally representative population from Sweden, the prevalence of olfactory dysfunction was 19.1%, with nearly 6% of participants designated as anosmic.[15] Notably, self-reports of "worse-than-normal" olfaction was 15.3% in the same population.[16] An Australian investigation of participants from in and around Sydney, utilizing the San Diego Odor Identification Test, identified impaired olfaction in 27% of participants.[17] In a Spanish study, participants were given four microencapsulated odorants and asked to correctly detect, recognize, and identify each odorant. Prevalence of impaired detection was 19.4%, with 0.3% of the population reported as anosmic. Meanwhile, 43.5% (0.2% anosmic) and 48.8% (0.8% anosmic) of the population were designated as having impaired olfactory recognition and identification, respectively.[18]

Multiple US-based studies have utilized both self-reporting and psychophysical testing. In a large cohort of participants from Wisconsin, olfactory dysfunction was identified in 24.5% of all participants, and 62.5% of participants over the age of 80, as defined by the San Diego Odor Identification Test.[4] Additional US-based studies examining aged populations with various psychometric olfactory instruments have reported rates of olfactory dysfunction from 2.7-100%, with significant variation regarding the definitions of dysfunction, study size, participant demographics and age.[19-25]

Overall, olfactory dysfunction is a common condition, with a wide range of prevalence across population-based studies. Accurate population-level incidence and prevalence rates are challenging to fully elucidate, but appear to be higher in more elderly persons and males.

SECTION: VII. Pathophysiology

A. Sinonasal Inflammatory Disease

1. Basic underlying mechanisms

Sinonasal inflammatory disease is the most common cause of olfactory loss.[1–3] Olfaction relies on conduction of odorants from the air to the olfactory epithelium (OE) and subsequent sensorineural signaling to the brain. Clinical and basic science research suggests that disruption of both of these mechanisms contributes to olfactory dysfunction (OD) in the setting of sinonasal inflammation.

Sinonasal mucosal inflammation, and especially nasal polyposis, results in a conductive olfactory loss from physical obstruction of airflow and anterograde restriction of odorants from accessing the olfactory cleft (OC).[4,5] Increased resistance to airflow has been associated with decreased perception of odor strength[6] that improves with nasal valve dilation.[7] Computational fluid dynamics in patients with in chronic rhinosinusitis (CRS) with nasal polyps has shown variation in airflow disruption based on polyp location that correlates to degree of OD, with the greatest dysfunction in patients with OC polyps and the least dysfunction with polyps confined to the middle meatus.[8,9] Similarly, OC opacification on CT, reflective of OC patency, has been shown to correlate with OD differentially by CRS type.[10,11] Removal of obstruction either through surgical[12–14] or anti-inflammatory[15,16] treatment results in similar levels of improvement in olfaction. Additionally, chronic inflammation has been speculated to alter olfactory mucus composition, impeding conduction of odorants.[17]

While airflow patency plays an important role, it does not fully correlate with the degree of olfactory loss in sinonasal inflammatory disease[18–20], suggesting the contribution of other mechanisms. In contrast to conductive loss, sensorineural OD involves disruption of olfactory sensory neuron (OSN) signaling and processing. The pseudo-stratified OE is comprised of multiple neuronal and non-neuronal cell types that may be affected by inflammation. Its location in the nasal airway makes it vulnerable both to direct injury from exogenous inflammatory stimuli, as well as secondary injury from endogenous antimicrobial defenses of the adjacent respiratory mucosa. Although this damage disrupts OE integrity and function, the OE has a remarkable ability to regenerate, with mitotically active globose basal cells continuously replacing OSNs and maintaining the apical non-neuronal barrier.[21–23] Horizontal basal cells (HBCs) provide a secondary, quiescent stem cell pool that is activated after severe injury.[24,25] The signaling pathways that guide regeneration are incompletely understood, but

include p63 and Notch[26–28] in mice, and appear to be modulated by inflammatory mediators such as TNF[29–35] and NF-κB-mediated cross-talk between HBCs and immune cells.[36,37] In animal models, exposure of the OE to bacteria or allergens produces an influx of inflammatory cells associated with neuronal loss and decreased renewal of immature olfactory neurons,[37–41] with similar findings noted in specimens from anosmic patients.[42–45] Markers of inflammation, such as tissue eosinophilia[45,46] and the presence of type 2 cytokines in mucus obtained from the olfactory cleft,[19,47–51] have been reported to correlate with olfactory loss in CRSwNP.

In summary, the OE is impacted by, and likely participates in, sinonasal inflammatory disease, with varying contributions of conductive and sensorineural mechanisms on olfactory function and OE structure. Medical therapy that targets inflammation likely improves olfaction both by increasing airflow and by reducing local inflammatory cells and mediators.[3,12,16,52] The expression of steroid receptors on OE cells [53,54] in animal models and the attenuation of OE lesions after topical administration of steroids may suggest additional direct effects of corticosteroids on OE function.[55] Irreversible olfactory loss after longstanding sinonasal inflammatory disease may be a result of neurogenic exhaustion or metaplastic changes to the OE. While reduction of sinonasal inflammation remains the primary treatment strategy, future therapies may target neuroprotective mechanisms or activation of progenitor cell-mediated regeneration.[56,57]

Table VII.1. Section Evidence Summary Table: Sinonasal Disease; Basic Underlying Mechanisms

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical Endpoint	Conclusion
Youngentob et al[6]	1986	4	Case series	10 healthy controls (HC)	• Perceived odorant intensity • Perceived sniffing effort	Olfactory magnitude decreases with increased nasal resistance
Seiden et al[3]	2001	3	Prospective cross-sectional	All-comers with change in smell / taste	• UPSIT	Etiology of olfactory loss may help guide prognosis and

				perception (n=420)		response to steroids
Lane et al[18]	1996	3	Prospective case series	Pollen-sensitive subjects (n=8)	• Nasal patency • UPSIT	Alterations in nasal patency do not correlate with olfactory function
Klimek et al[19]	1997	2	Prospective case-control	Grass allergy (n=17), HC (n=12)	• Nasal volume flow (NVF) • Eosinophil cationic protein (ECP) • CCCRC	Decrease in olfaction during allergy season correlated to ECP but not NVF
Lee et al[42]	2000	5	In vitro	18 explants from 6 normosmic patients, 45 explants from 15 anosmic	• Map5 • Cellular morphology • T&T olfactometry	Significantly decreased number of olfactory receptor cells and abnormal morphology in anosmic specimens
Kern[43]	2000	5	In vitro	120 OE explants (26 CRS, 4HC)	• UPSIT • Histologic inflammatory changes	OE has a similar inflammatory infiltrate in CRS as respiratory epithelium; inflammatory changes may contribute to olfactory deficit
Stevens[12]	2001	4	Prospective case series	24 CRSwNP with anosmia	• UPSIT	Surgery resolved anosmia in 12/24; oral but not intranasal steroid sprays improved anosmia in 9/12 remaining patients

Hornung et al[7]	1997	4	Case series	12 HC	• SS	Use of nasal dilators increases odorant identification and intensity and decreases threshold
Landis et al[5]	2003	2	Prospective case-control	HC (n=56) vs CRSwNP (n=42)	• SS • Odorized powder identification	Retronasal olfactory function is retained over orthonasal in the presence of nasal polyps in the anterior portion of the OC
Pfaar et al[4]	2006	1	Randomized controlled trial	Healthy controls with sponges in olfactory cleft (n=20) or respiratory epithelium (n=13)	• SS • Odorized powder identification	Orthonasal but not retronasal odor indentification is significantly decreased after obstruction of the olfactory cleft
Zhao et al[8]	2006	4	Case report	1 CRSwNP	• CFD olfactory airflow • Odorant delivery rate • Psychophysical olfactory assessment	Surgical remodeling of the nasal airway is a significant factor in recovering olfactory function
Yee et al[44]	2010	3	Prospective case control	CRS (n=50) HC (n=20)	• PEA threshold test • Histological analysis of neuronal, nonneuronal, inflammatory cells • UM Staging System	CRS patients demonstrated metaplasia and lower percentages of normal epithelium and olfactory sensory neurons; CRS patients with anosmia most likely to have OE erosion, highest

						density of eosinophils, and most extensive abnormalities on CT
Hox et al[20]	2010	3	Prospective study	CRSwNP (n=65)	• VAS • SNOT-22 • SF-36 • PNIF • SS • Eosinophilia	Olfaction correlates to blood eosinophilia but not PNIF or VAS for obstruction
Selvaraj et al[17]	2012	3	Prospective crossover	11 HC	• SS	Nasal irrigation with an ion concentration that mimics mucus composition in chronic inflammation induces a significant elevation of olfactory thresholds
Mori et al[11]	2013	3	Prospective cross-sectional	228 CRS, 190 ECRS	• T&T • Intravenous olfactory test • Likert scale • Ethmoid opacification • OC polyps	Olfactory dysfunction more severe in ECRS; ethmoid opacification and OC polyps were associated with olfactory dysfunction in CRS
Henkin et al[49]	2013	3	Retrospective case-control	59 hyposmia, 6 HC	• IL-6 levels in urine, saliva, nasal mucus	IL-6 in nasal mucus, plasma, and saliva is significantly higher in hyposmic patients than controls and may have a role in the pathogenesis on a local or systemic level
Banglawala et al[52]	2014	1	Meta-analysis	4 RCTs of subjective	• SF-36 • Pocket smell	Oral steroids significantly improve

				olfaction after oral steroids in CRSwNP (n=236) 2 RCTs of objective olfaction after oral steroids in CRSwNP (n=147)	test • BSAT-24	subjective and objective measures of olfaction in CRSwNP.
Alobid et al[16]	2014	2	RCT	Moderate to severe CRSwNP, steroid tx (n=67) control (n=22)	• BSAT-24 • Likert • Polyp tissue eosinophilia • Nasal nitric oxide • Lildholdt score • Lund Mackay	Oral and intranasal steroids improve olfaction in CRSwNP; loss of olfaction is correlated with nasal congestion but not inflammation
DeConde et al[15]	2014	3	Prospective cross sectional	CRS patients treated medically (n=58) and surgically (n=222)	• B-SIT • RSDI • SNOT-22 • Lund Mackay	Surgical treatment of CRS results in similar improvement in olfaction to continuation of medical therapy
Schlosser et al[48]	2016	3	Prospective cross-sectional	CRSwNP (n=15) CRSsNP (n=19)	• SS • Cytokine bead assay	IL-5 levels were inversely correlated with all CRS patients, whereas IL-6, IL-7 and VEGF levels were positively correlated only in CRSwNP
Hauser et al[46]	2017	3	Prospective case-control	CRSwNP (n=32) CRSsNP (n=27) HC (n-10)	• UPSIT • Lund Mackay • SNOT-22	Tissue eosinophilia is associated with olfactory loss in CRSwNP independent

					• Tissue eosinophilia	of disease severity
Lavin et al[45]	2017	3	Prospective case control	CRSwNP (n=36) CRSsNP (n=37) HC (n=26)	• UPSIT • OC opacification • CLC • ECP	Markers of eosinophils are elevated in the superior turbinate of CRS patients and correlate with olfactory loss
Wu et al[47]	2018	3	Prospective case-control	CRSwNP (n=36) CRSsNP (n=31) HC (n=12)	• UPSIT • Cytokine bead assay	The inflammatory microenvironment in the OC mirrors that in the middle meatus; Elevation in IL-2, IL-5, IL-6, IL-10, IL-13 are correlated with reduced olfactory scores
Nishijima et al[9]	2018	4	Case series	CRSwNP (n=21) HC (n=4)	• CFD olfactory airflow • Odorant uptake • T&T	Olfactory airflow and olfaction are differentially affected by nasal polyp location
Victores et al[56]	2018	5	In vitro	CRS (n=11), HC (n=9)	• Expression of phosphorylated c-Jun	Explants from CRS patients demonstrated increased phosphorylated c-Jun in olfactory neurons with an associated loss of neurons
Valsamidis et al[14]	2019	3	Prospective case-control	60 septal deviation, 25 HC	• SS • NOSE • QOD	Septoplasty leads to improvement in smell perception and

						improved QOL
Chen et al[37]	2019	5	In vitro	32 CRS OE explants, 17 HC OE explants	• $CD45^+$ and $CD3^+$ • Beta-tubulin III • $Krt5^+$ $p63^+$ • CCL20	Olfactory stem cell switching occurs in human models of inflammation to promote immune defense over regeneration
Morse et al[50]	2019	3	Prospective cross-sectional	CRSwNP (n=61) CRSwNP (n=49)	• UPSIT • Lund Mackay • Inflammatory cell counts • OC cytokine bead assay	Hierarchical cluster analysis reveals olfactory dysfunction is associated with specific CRS endotypes characterized by severe nasal polyposis, tissue eosinophilia, and AERD. Mucus IL-2 levels, CT score, and AERD were independently associated with smell loss
Loftus et al[10]	2020	2	Prospective case-control	CRSsNP (n=73) CRSwNP (n=75) HC (n=30)	• SS • Lund Mackay	Olfactory dysfunction correlates with OC opacification and Lund-Mackay score in CRSwNP but not CRSsNP
Soler et al[51]	2020	3	Prospective cross-sectional	CRSwNP (n=37) CRSsNP (n=25)	• SS • Lund Mackay • OC	Th2-related inflammatory proteins are more often found

					• opacification • OC cytokine bead assay	in OC mucus of CRSwNP and correlate with olfactory dysfunction and opacification on CT

UPSIT – University of Pennsylvania Smell Identification Test; CCRC - Connecticut Chemosensory Clinical Research Center; T&T – Toyota and Takagi olfactometry; SS – Sniffin' Sticks; CFD – computational fluid dynamics; PEA threshold test – Phenyl Ethyl Alcohol smell threshold test; VAS –visual analogue scale; SF-36 –Short-form health survey; PNIF –peak nasal inspiratory flow; BSAT-24 –Barcelona Smell Test-24; B-SIT -Brief Smell Identification Test; RSDI – rhinosinusitis disability index; CLC –Charcot Leyden crystal protein; NOSE -nasal obstruction symptom evaluation; QOD – Questionnaire of olfactory deficits.

Sinonasal inflammatory disease as a cause of olfactory dysfunction

Aggregate Grade of Evidence: B (Level 1: 1 study, Level 2: 1 study, Level 3: 9 studies, Level 4: 1 study)

Decreased odorant conduction as a mechanism of inflammation-associated olfactory dysfunction

Aggregate Grade of Evidence: B (Level 1: 1 study, Level 2: 3 studies, Level 3: 3 studies, Level 4: 5 studies)

Sensorineural mechanisms as underlying cause of inflammation-associated olfactory dysfunction

Aggregate Grade of Evidence: C (Level 3: 3 studies, Level 5: 4 studies)

SECTION: VII. Pathophysiology

A. Sinonasal Inflammatory Disease

1) Related to CRS

a) In relation to phenotype (NP or no NP)

The degree of olfactory dysfunction commonly varies by CRS phenotype, with CRSwNP usually demonstrating a higher prevalence and severity of olfactory impairment than CRSsNP.[1–6] The factors contributing to olfactory loss in CRS are complex and likely a consequence of multiple pathophysiological mechanisms that may differ depending on phenotype. Mechanical obstruction of odorant transmission to the olfactory cleft neuroepithelium can be a result of mucus, edema, and/or nasal polyps and is usually more severe in CRSwNP.[7,8] As noted in the prior section, in this mechanism, the polyps and edema characteristic of the CRSwNP

phenotype block odorants from reaching the olfactory cleft. Among CRSwNP, olfactory cleft opacification on CT scan correlates with the severity of olfactory dysfunction.[9] Differences in orthonasal versus retronasal olfactory function have been demonstrated, with retronasal olfactory function better preserved compared to orthonasal function among CRSwNP.[9,10] Patients with CRSsNP tend to have less olfactory cleft opacification on CT scan, suggesting less disruption of odorant delivery as compared to CRSwNP.[9] Direct inflammation at the level of the neuroepithelium is another possible mechanism of CRS-related olfactory loss.[11] In this mechanism, odorants may reach the olfactory cleft but inflammatory changes of the neuroepithelium disrupt transduction. In CRSsNP animal models where inflammatory mediators such as tumor necrosis factor alpha (TNF-alpha) were directly induced in olfactory inflammation, neuronal cell death and inhibition of olfactory epithelium proliferation were observed.[7,8] This neuroepithelial inflammation was temporary, and resulted in reversible interference in odorant transduction. In CRSwNP, mucosal inflammation and tissue eosinophilia (>5 eosinophils/HPF) have been associated with worse objective olfactory function at baseline.[11] Following sinus surgery, improvements have been reported among patients with nasal polyposis and eosinophilia .[12–14] As covered in the section to follow on endotyping, studies have also found correlation between olfaction and the level of inflammatory proteins found in olfactory cleft mucus, including IL5, IL13, and IgE among others. Although these inflammatory proteins are most commonly seen in CRSwNP, they may also be elevated in CRSsNP, suggesting that phentoypes are not always reflective of underlying endotype.[11] Olfactory cleft neuroepithelium remodeling represents another potential mechanism for CRS olfactory loss.[15] Biopsy of the olfactory cleft in patients with chronic inflammation has shown changes to the neuroepithelium, with resulting squamous metaplasia, fibrosis or replacement of the olfactory epithelium with respiratory epithelium.[16–18] Several studies have also found associations between olfaction and olfactory bulb remodeling.[18,19] When examining objective disease burden among CRSsNP, higher severity of sinonasal inflammation has been associated with smaller olfactory bulb volumes and decreased retronasal olfactory function.[19] Inflammatory-related changes in the olfactory neuroepithelium as previously described are postulated to result in decreased sensory input to the olfactory bulb resulting in a decrease in olfactory bulb

volume. Additionally, among CRSwNP, changes in olfactory bulb volumes have been examined in response to medical and surgical treatment with a correlation observed between improvement in olfactory function and increase in olfactory bulb volume.[20]

Table VII.2. Section Evidence Summary Table: CRS; in relation to Phenotype

Study	Year	LOE	Study design	Study group	Clinical endpoint	Conclusion
Wu[21]	2018	3b	Case-control study	CRS (n = 67) CRSwNP (53.7%) CRSsNP (46.3%) Healthy controls (n = 12)	Olfactory testing immediately prior to surgery (Smell Identification Test) Olfactory mucus protein analysis	Olfactory function and inflammatory mediators were largely dependent on polyp status Mucus protein levels [cytokines (IL-2, IL-5, IL-6, IL-10, IL-13)] inversely correlated with olfactory function by identification testing among the overall cohort IL-2, IL-5, IL-6, and IL-10 showed a negative correlation with olfactory function among CRSsNP, however this was not statistically significant IL-5 and IL-13 were independent predictors of olfactory function among all patients Elevated levels of IL-5 and IL-13 among CRSwNP compared to CRSsNP

Kern[22]	2009	3b	Case-control study	CRS (n = 26) Healthy controls (n = 4)	Biopsy olfactory mucosa for histopathologic analysis Preoperative olfactory testing (UPSIT)	Nineteen biopsy specimens had olfactory mucosa 9 patients had normal olfactory mucosa and normal olfactory function (UPSIT > 35) 10 patients had pathologic changes in olfactory mucosa with 7 of these patients having olfactory deficits 3 patients had normal olfactory function despite moderate chronic inflammation
Soler[23]	2020	4	Cross-sectional study	CRS (n = 62) CRSwNP (59.7%) CRSsNP (40.3%)	Olfactory testing (Sniffin Sticks) Olfactory mucus protein analysis Lund-Mackay CT score	Correlations between mucus proteins and olfaction function persisted after stratifying for polyp status Olfactory loss in some patients with CRSwNP may result from direct inflammation of OC mucosa as opposed to alterations in nasal airflow from nasal polyposis

Hauser[24]	2017	3b	Case-control study	CRS (n = 59) CRSwNP (54.2%) CRSsNP (45.8%) Health controls (n = 10)	Olfactory testing immediately prior to surgery (Smell Identification Test) Histopathological evaluation of ethmoid bulla (CRS); and ethmoid sinus or sphenoid face (controls)	CRSwNP was associated with higher mean tissue eosinophil counts (71.6 vs. 28.1 eosinophils/HPF, $p<0.05$) and lower age/sex-adjusted SIT scores (−17.4 vs. −6.2, $p<0.001$) when compared to CRSsNP SIT scores were strongly negatively correlated with tissue eosinophil counts in CRSwNP ($r=-0.60$, $p=0.0003$), but not CRSsNP ($r=0.16$, $p=0.42$)
Ganjaei[25]	2018	4	Case series	CRS (n = 70) CRSwNP (58.5%) CRSsNP (41.4%)	Olfactory testing: retronasal and orthonasal (Sniffin Sticks)	Higher prevalence of anosmia among CRSwNP vs. CRSsNP, as well as lower mean TDI scores, mean retronasal olfaction scores, worse endoscopy and OC scores Lower odor threshold, odor discrimination, and odor identification scores among CRSwNP vs. CRSsNP Retronasal identification was worse among CRSwNP vs. CRSsNP

Othieno[26]	2018	4	Case series	CRS (n = 69) CRSwNP (58.0%) CRSsNP (42.0%)	Olfactory testing: retronasal and orthonasal (Sniffin Sticks) OC endoscopy score	Strong correlation between retronasal and total orthonasal olfaction scores among all patients ($r = 0.77$, $p < 0.001$) Retronasal olfaction scores worse among CRSwNP OC endoscopy score independently predicted retronasal olfaction ($r = -0.42$, $p < 0.001$), suggesting that inflammation or blockage of OC drives olfactory loss rather than changes in airflow alone
Lavin[27]	2017	4	Cross-sectional study	CRS (n = 73) CRSwNP (49.3%) CRSsNP (50.7%) Health controls (n = 26)	Olfactory testing (Sniffin Sticks and UPSIT) obtained in a subset of patients Tissue biopsies Gene expression CLC CT and endoscopic analysis	Superior turbinate tissue of CRSwNP patients had significantly increased eosinophilic inflammation and olfactory threshold deficits were significantly associated with nasal polyp status, as well as superior turbinate eosinophilia, even after controlling for nasal polyp status

Soler[11]	2009	4	Cross-sectional study	CRS (n = 147) CRSwNP (44.9%) CRSsNP (55.1%)	Smell Identification Testing (SIT) Mucosal histopathologic findings (ethmoid cavity)	Higher mucosal eosinophil counts correlated with worse SIT scores (r = -0.253; p = 0.002) Mucosal eosinophils (>5/HPF) present in 66.7% of CRSwNP Lower SIT in eosinophilic-CRSwNP compared to non-eosinophilic-CRSwNP (19.3 ± 11.3 vs. 25.1 ± 9.8; p < 0.001) No correlation between mucosal eosinophil counts and SIT scores among CRSsNP
Gudziol[20]	2009	4	Case series	CRSwNP (n = 19) Healthy controls (n = 18)	Preoperative and 3 month postoperative olfactory testing (Sniffin' Sticks), MRI volumetric measurement of olfactory bulb	Increase in olfactory bulb volume following surgery correlated with odor thresholds (left side r = 0.60, p = 0.005; right side r = 0.49, p = 0.03), but not with odor discrimination or odor identification No change in olfactory bulb volume nor olfactory testing among control group

Rombaux[19]	2008	4	Case series	CRSsNP (n = 22) Healthy controls (n = 16)	Olfactory testing: retronasal and orthonasal (Sniffin' Sticks) MRI volumetric measurement of olfactory bulb Lund-Mackay score	No difference in olfactory bulb volume among CRSsNP vs. controls Olfactory bulb volume was inversely correlated with Lund-Mackay score (r = -0.52, p = 0.001), scores ≤ 12 had larger olfacatory bulb volumes compared to scores > 12) Higher Lund-Mackay score correlated with worse retronasal olfactory function (r = -0.040, p = 0.014), but not with orthonasal olfactory function
Landis[10]	2003	4	Case series	CRSwNP (n = 42) Healthy controls (n = 56)	Olfactory testing: retronasal and orthonasal (Sniffin Sticks)	Better retronasal than orthonasal olfactory function in presence of anterior OC obstruction with CRSwNP No difference between retronasal and orthonasal smelling among controls

SECTION: VII. Pathophysiology

A. Sinonasal Inflammatory Disease

1) Related to CRS

b) In relation to endotype

CRS has been traditionally classified based on clinically observed phenotype,[1] e.g., the presence (CRSwNP) or absence (CRSsNP) of nasal polyps, the presence of aspirin-sensitivity (AERD), or the presence of fungal elements in allergic fungal sinusitis.[2–5] The CRSwNP and AERD phenotypes have significantly higher prevalence of olfactory dysfunction, as previously discussed. However, in recent years, there has been a research push toward classifying CRS into endotypes unified by common pathobiological or molecular mechanism rather than clinically observed characteristics. These efforts are motivated in part by the new availability of precision biologic drugs that target specific mechanisms of inflammation in CRS. Additionally, there is evidence that certain phenotypes like CRSwNP may have significant endotypic heterogeneity in different parts of the world.[6–8] Of particular interest to olfactory outcomes in CRS has been the ability of monoclonal antibodies against Type 2 inflammation (previously known as Th2 inflammation) to improve olfactory function in CRSwNP . Clinical trials studying these medications allow insight into mechanisms driving CRS-associated olfactory loss. This section will summarize endotyping studies in CRS that have specifically evaluated olfaction with mention of randomized controlled studies of precision biologics that report olfactory outcomes.

A number of studies have examined tissue and mucus biomarkers from the olfactory cleft of patients with CRS, mostly in a cross-sectional fashion (**Table VII-3**). In terms of endotyping, several studies have reported measurement of individual cytokines, chemokines and or cellular products and their relationship to olfaction,[9–12] whereas one study utilized supervised or unsupervised mechanisms to dimensionally reduce inflammatory mediators and classify patients into clusters organized by commonalities in their inflammatory profile.[13] The latter method of analysis, while commonly thought of as endotyping, does not always produce pathogenically unifying clusters, as a single cluster can be identified by multiple mechanisms. From these studies, Type 2 cytokines such as IL-5 and IL-13, as well as markers of eosinophilia, measured in olfactory tissue or in secretions in the olfactory cleft appear consistently related with olfactory dysfunction as measured using both Smell Identification Test (SIT) and Sniffin' Sticks measurements. In the studies that have utilized larger panels of inflammatory mediators, IL-6 and IL-10 cytokines in olfactory mucus, which are not traditionally considered Type 2 cytokines, have also been associated with olfactory dysfunction in more than one independent

study.[11,12] While these studies do elucidate inflammatory mediators present in the olfactory cleft among patients with olfactory dysfunction, they do not provide a mechanistic understanding of how Type 2 inflammation causes olfactory loss. Evidence does suggest that at least some of the olfactory loss is conductive in nature, as the identified inflammatory factors are also correlated with edema in the narrow olfactory cleft as measured by radiographic opacification.[12] Interestingly, in the studies that have separated analyses out by CRSsNP and CRSwNP phenotypes, the associations between endotype and olfactory function appear significant primarily among patients with CRSwNP, suggesting that the effects of Type 2 inflammation explain a greater portion of the variance in olfactory function among these patients.[12] Currently, there are no studies which have utilized endotyping approaches to predict olfactory outcomes after surgery however, a recent study found that eosinophilic inflammation in the superior turbinate was predictive of olfactory deficit after 3-months sinus surgery.[14]

The two biologic medications specifically targeting aspects of Type 2 inflammation in CRSwNP included objectively measured olfaction as an endpoint.[15–17] These will not be discussed in detail here, but the improvements observed relative to placebo nonetheless provide definitive evidence that Type 2 inflammation is mechanistically important to olfactory deficit. Dupilumab which targets the common receptor of IL-4 and IL-13 is known to inhibit lymphocyte differentiation and lineage commitment and plays a role in Th0 to Th2 differentiation, B-cell isotype switching to IgE, and antibody secretion and differentiation of epithelial cells into mucus secreting cells.[18,19] Omalizumab, in contrast, targets soluble and cell bound IgE. Evidence that both these precision biological medications improved olfactory outcomes in CRSwNP patients relative to placebo provides evidence that these inflammatory effects directly or indirectly cause olfactory deficit and provide impetus for endotyping based approaches to study CRS associated olfactory loss.

Table VII.3. Section Evidence Summary Table: CRS; in relation to Endotypic Factors

Study	Year	LOE	Study design	Studied population	Sample studied and olfactory testing method	Endotypic factors associated with olfactory findings

Schlosser[9]	2016	2	Cross-sectional	34 patients; 19 CRSsNP, 15 CRSwNP.	-Olfactory cleft mucus - Sniffin' Sticks	IL-5 was associated with worse overall T/D/I score and identification.
Lavin[10]	2017	2	Cross-sectional	30 patients; 7 control, 10 CRSsNP, 13 CRSwNP	Superior Turbinate tissue -UPSIT and Sniffin' Sticks (threshold) prior to ESS	Charcot Leyden Crystal Protein (CLC) gene expression was associated with worse UPSIT and threshold scores.
Wu[11]	2018	2	Cross sectional	67 patients; 31 CRSsNP, 36 CRSwNP	-Olfactory cleft mucus -UPSIT prior to ESS	IL-2, IL-5, IL-6, IL-10 and IL-13 were significantly associated with SIT scores
Morse[13]	2019	2	Cross sectional	110 patients; 49 CRSsNP, 61 CRSwNP.	-Middle Meatal Mucus -SIT prior to ESS	A cluster characterized by high IL-5 and IL-13 levels had significantly higher objective olfactory deficit. However, IL-5 and -13 alone were not independently associated when AERD status, CT score were modeled.
Wu[14]	2020	2	Longitudinal after sinus surgery	76 patients; 36 CRSsNP, 30 CRSwNP	-Superior Turbinate mucosa -Sniffin' Sticks	Pre-operative eosinophilia was associated with objective olfactory decline.

Soler[12]	2020	2	Cross-sectional	62 patients; 25 CRSsNP, 37 CRSwNP patients	-Olfactory cleft mucus -Sniffin' Sticks	IL-5,IL-6,IL-13,IL-9, IL-10, IL-23, CCL2, CCL3 and IgE were associated with T/D/I score. Correlations between inflammatory mediators and olfaction only observed among CRSwNP patients.

- **CRS Endotyping is Associated with Olfactory Function**

  Aggregate Grade of Evidence: C (Level 4: 5 studies)

SECTION: VII. Pathophysiology

A. Sinonasal Inflammatory Disease

2) Related to allergic rhinitis or chronic rhinitis

Extensive evidence supports the association between rhinitis and olfactory dysfunction (OD), although the prevalence of OD in patients with rhinitis varies significantly in the literature. In a large population study in Sweden, subjective hyposmia was reported by approximately 30% of those with non-allergic rhinitis (NAR), 13% in allergic rhinitis (AR), and 12% in healthy individuals.[1] In South Korea, a diagnosis of OD was strongly associated with AR compared to healthy individuals (odds ratio=4.88).[2] In a systematic review of 36 studies, OD was observed in 10-90% of patients with AR, with most studies reporting between 20-40%.[3] This finding is corroborated across pediatric populations; one study identified a significant increase in OD only for pediatric patients whose symptoms exceed 3 years.[4–7] One explanation for the wide range of OD in this population is that some studies have included patients with comorbid chronic rhinosinusitis.

A variety of subjective and objective metrics have been utilized to assess olfactory function in patients with rhinitis. The severity of OD is typically within the mild-to-moderate range; true anosmia is rare.[3,8,9] Patients with perennial AR or NAR exhibit symptoms of OD year-round. On the other hand, patients with seasonal AR exhibit hyposmia during allergy season with normalization of odor discrimination and identification extra-seasonally, but they appear to demonstrate persistently depressed odor thresholds.[4,10,11] Suzuki et al[12] demonstrated that patients with seasonal AR for ≥10 years, in particular, suffer from extra-seasonal OD.

Fewer studies specifically investigate the effects of NAR on olfaction. Some evidence suggests higher rates and more severe OD in patients with NAR compared to patients with AR, but this finding is inconsistent across the published literature.[1,7,13,14]

Two primary mechanisms have been proposed to explain the OD observed in patients with rhinitis. OD may be secondary to an obstructive phenomenon leading to reduced airflow through the olfactory cleft.[15] However, the literature more strongly supports the notion that inflammatory cytokines detrimentally affect the function of the olfactory mucosa.[4,11,14–16] Murine models of AR have demonstrated OD secondary to infiltration of eosinophils, mast cells, plasma cells, macrophages, and neutrophils in the olfactory epithelium.[17–19] A study by Kim et al[18] demonstrated that mice with AR exhibited higher rates of olfactory stem cell apoptosis induced by TNF-alpha with a synergistic effect from interleukin-5.

In summary, the literature strongly supports the association between rhinitis and OD with variable incidence and severity depending on the subtype of rhinitis and selection of study population.

Table VII.4: Section Evidence Summary Table: Allergic or Nonallergic Rhinitis

Study	Year	LOE (1 -5)	Study Design	Study Groups	Clinical End-point	Conclusion
Olsson *et al.*	2003	2	Cross sectional study	1) 10,670 adults	1) Self-reported questionnaire	In a population study, 19% of individuals reported symptoms consistent with NAR, while 24% reported AR. Subjective hyposmia was reported by approximately 30% in NAR, 13% in AR, and 12% in healthy individuals.

Rhee *et al.*	2014	2	Cross sectional study	1) 2305 participants	1) IgE testing 2) Health survey	Prevalence of AR 16%. Odds ratio of olfactory dysfunction for those with AR 4.88 compared to healthy population.
Stuck & Hummel	2015	2*	Systematic review	1) 36 studies N range (17-10,670 patients)	1) Effect of AR on olfaction	OD in AR ranges from 20-40%, typically mild to moderate.
Aksoy *et al.*	2018	3	Case control study	1) 44 pediatric patients with seasonal AR	1) CCCRC (odor discrimination, identification, threshold) 2) Subjective olfactory assessment 3) Acoustic rhinometry 4) Allergy prick testing	CCCRC scores significantly decreased during allergy season, which correlated with subjectively reported hyposmia. Nasal volume decreased during allergy season, but no correlation between CCCRC score and acoustic rhinometry.
Mariño-Sanchez *et al.*	2018	4	Cross sectional study	1) 142 pediatric patients with persistent AR	1) Self-reported VAS	Self-reported OD in pediatric patients with AR is associated with severe and uncontrolled disease.
Langdon *et al.*	2016	3	Cross sectional study	1) 1,260 pediatric patients with AR (CRS not excluded)	1) Questionnaire with self-reported symptoms	44% of patients exhibited self-reported OD, which was positively correlated with the severity of disease.
Kutlug *et al.*	2016	4	Case control study	1) Control group – 45 pediatric patients 2) AR – 42 pediatric patients 3) NAR – 35 pediatric patients	1) Sniffin' Sticks (odor identification and discrimination)	No significant difference in odor scores between groups or based on severity. However, odor identification and total odor scores were lower in patients with symptoms for >3 years.
Katotomichelakis *et al.*	2015	3	Cross sectional study	1) Control group – 48 healthy patients 2) Placebo-control	1) Sniffin' Sticks (odor discrimination,	At baseline, 67.9 % of patients were normosic, 23.7% were hyposmic and 8.4% were anosmic. Patients with AR exhibited lower olfactory related QoL scores compared with healthy controls.

				group – 45 patients with AR 3) Treatment group – 145 patients with AR	identification, threshold) 2) Questionnaire of Olfactory Deficits 3) QoL surveys	
Klimek *et al.*	2017	4	Case series	1) 47 patients with persistent AR	1) Sniffin' Sticks (odor discrimination, identification, threshold)	Mean baseline TDI score of the cohort was 23.7 (±3.9), consistent with hyposmia (≤30.5).
Moll *et al.*	1998	4	Case control study	1) 28 patients with seasonal AR 2) 47 patients with perennial AR 3) Control group – 66 healthy patients	1) CCCRC (odor discrimination, identification, threshold)	When tested intraseasonally, both patients with perennial and seasonal AR exhibited OD as compared to controls. Extraseasonally, only odor threshold testing was significantly lower in patients with seasonal AR as compared with controls.
Klimek & Eggers	1997	4	Case control study	1) 17 patients with AR (grass pollen) 2) Control group – 12 healthy patients	1) CCCRC (odor discrimination, identification, threshold) 2) Nasal volume flow 3) Eosinophilic cation protein levels	Odor discrimination and identification similar in AR and control patients preseasonally, but odor thresholds decreased in AR group. Intraseasonal testing revealed OD in AR group, which correlated with nasal eosinophilic cation protein levels.
Suzuki *et al.*	2018	4	Case control study	1) 50 control subjects 2) 50 subjects	1) Odor Identification (Open Essence	OD existed in >50% of subjects with AR for ≥ 10 years. OD exists extraseasonally in patients with AR for ≥ 10 years.

				3) with AR <10 years 3) 50 subjects with AR ≥10 years	test) 2) Odor Detection 3) Odor Threshold	
La Mantia *et al.*	2018	4	Case control study	1) AR – 50 patients 2) NAR – 40 patients 3) Mixed Rhinitis – 32 patients	1) Sniffin' Sticks (odor discrimination, identification, threshold)	Patients with NAR exhibited a significantly lower TDI score consistent with greater OD as compared to patients with AR or mixed rhinitis.
Guss *et al.*	2009	4	Case control study	1) 31 patients with AR 2) 10 patients with AR + CRS 3) 10 patients with NAR	1) UPSIT 2) CT Sinus 3) Allergy Prick Testing	50% of patients with AR exhibited hyposmia. No significant difference between patients with CRS in addition to AR. Patients with NAR had a lower UPSIT score (p=0.06).
Sivam *et al.*	2010	2	RCT	1) Placebo control group – 9 patients with AR 2) Mometasone treatment group – 8 patients with AR	1) Nasal symptoms 2) UPSIT 3) Histopathology exam of olfactory epithelium	Of 17 patients with AR, 12 exhibited mild to moderate OD at baseline, 2 were anosmic, and 3 had normal olfactory function.
Becker *et al.*	2012	4	Case control study	1) Seasonal AR – 23 patients 2) Perennial AR – 16 patients 3) Control group – 33 patients	1) Sniffin' Sticks (odor discrimination, identification, threshold) 2) Nasal secretion analysis 3) Inspiratory nasal flow	No significant difference in inspiratory nasal flow between groups. Perennial and seasonal AR groups had significantly lower TDI scores. Eosinophilic protein levels and tryptase significantly higher in the seasonal AR group – no correlation with TDI score.

Jung & Hyo Kim	2020	2	RCT	1) Control group – 8 mice 2) Local nasal allergy - 8 mice 3) Systemic allergy - 8 4) Positive control - 8 mice 5) Budesonide treatment group - 8 mice	1) Odor detection 2) Histopathologic evaluation 3) Measurement of olfactory marker protein	Mice with AR from local intranasal and systemic sensitization demonstrated significant OD as measured by time to detect food pellets and on histopathologic exam.
Kim *et al.*	2019	2	RCT	1) Control Group – 25 mice 2) AR – 25 mice	1) Immunohistochemical staining	Mice with AR exhibit reduced numbers of olfactory sphere cells (neural stem cells) with increased apoptosis. TNF – alpha and IL-5 synergistically induce stem cell apoptosis.
Ozaki *et al.*	2010	2	RCT	1) Control group – 10 mice 2) AR group – 10 mice	1) Odor detection 2) Immunohistochemical staining	Mice with AR exhibit OD with increased size and number of olfactory glands. Infiltration of inflammatory cells observed, including eosinophils, mast cells, plasma cells, macrophages, and neutrophils.

*LOE downgraded due to heterogeneity of results and lack of RCTs.

- **Olfactory Dysfunction is Associated with Rhinitis**
  Aggregate Grade of Evidence: C (Level 2: 7 studies, Level 3: 3 studies, Level 4: 9 studies)

SECTION: VII. Pathophysiology

B. Post-Viral Loss

1) Non-COVID-19 related

Although COVID-19 is the most well-known viral cause of olfactory loss to the general public, olfactory experts have been treating post-viral olfactory dysfunction (PVOD) for years prior to the pandemic. The pathophysiology of PVOD following an infectious illness has not been clearly delineated.[1] As noted above, olfaction is a complicated process that includes many cellular and signaling pathways. As a result, there is a difference in the pathophysiology between olfactory loss in acute infectious processes and the more chronic PVOD. Nonetheless, studies have shown several key elements that may play a vital role in understanding how olfactory dysfunction occurs following a viral infection.

There are a multitude of viruses that have been shown to be present in the nasal respiratory epithelium of hyposmic/anosmic patients following a viral respiratory infection. These viruses include, but likely are not limited to, parainfluenza, Epstein-Barr virus, coronavirus, rhinovirus, influenza virus, respiratory syncytial virus, adenovirus, coxsackievirus, enterovirus, poliovirus, and herpes virus.[1–4] One recent study has shown rhinovirus and coronavirus to be the most commonly identified viruses in PVOD.[5] Viruses have been shown to damage a variety of cells within the olfactory system including olfactory receptor neurons which detect odorants and odorant binding proteins.[2] Other studies have shown that the olfactory neuroepithelium undergoes cellular changes due to viral insult.[1] These changes include the replacement of the neuroepithelium with respiratory-like epithelium, a highly disorganized olfactory epithelium compared to patients without olfactory dysfunction, and occasionally metaplastic squamous epithelium.[6,7] Other studies show that there is an increase in neurogenesis in response to the viral insult.[8] This results in a larger proportion of immature neurons compared to mature neurons, which may impact overall olfactory ability. Additionally, dendrites in the epithelium of patients with post-infectious olfactory disorders have been shown to be truncated and not able to reach the surface layer as would be seen in healthy tissue.[6–8] This may result in the inability of the neuroepithelium to detect odorants. Recent translational studies have shown that viruses may also cause indirect damage to olfactory cell function. These studies demonstrate that olfactory cells may clear viral elements without destroying them, and that viral elements can persist in nerve tissue.[9,10] The immune response and persistence of viral elements do not fully explain the observed changes to olfactory neuroepithelium nor the presence of PVOD in some patients compared to others. These studies suggest that viral infections drive olfactory dysfunction in varying ways depending upon the host's genetic makeup, immune response, and environment, so that there is not a clearly defined pathophysiological pathway at this time for all viral etiologies.

In addition to the previously mentioned viral effects on olfactory epithelium in relation to PVOD, there is also the acute onset of nasal congestion that hinders olfactory function that often accompanies a viral infection.[11] Nasal congestion limits the airflow across the olfactory epithelium, and without proper airflow, odorants are unable to be detected by the olfactory

epithelium. This process is acute and short-lived, and the sense of smell would theoretically return once the inflammation subsides. Unfortunately for some patients, olfactory dysfunction persists, likely due to neuroepithelial injury after this acute stage. The exact percentage of patients with persistent olfactory dysfunction is not well-defined because the total incidence of post-viral olfactory loss is not known, although this group makes up about 20-30% of most series accounting for etiology of olfactory dysfunction in patients presenting for treatment.[12] Nonetheless, 35-46% of patients with post-viral olfactory dysfunction will gain clinically significant improvement.[13] For those that do not recover, the pathophysiology of olfactory dysfunction may be a result of several underlying factors.

Post-infectious changes can extend further along the olfactory pathways. PVOD decreases the size of the olfactory bulb on imaging studies.[14] The volume of the olfactory bulb negatively correlates with the level of olfactory dysfunction.[15] It is unclear whether the olfactory bulb is decreasing in size due to the lack of neural input due to damage in the OE or if the olfactory bulb is decreasing as a direct impact from viral damage in the bulb itself.[16] Viral inoculation in the nostrils of mice have shown spongiotic damage to the olfactory bulb likely related to the infiltration of the bulb by lymphocytes and neutrophils. The olfactory bulbs in the inoculated mice were still decreased 5 months after injection.[8] Another study also showed direct cellular damage at the level of the olfactory bulb in mice when inoculated with the influenza virus.[17] This appears to be consistent with human imaging studies in patients with hyposmia/anosmia.

Another possible influence on PVOD is the host immune response to viruses. One study using a viral analog to induce an immune response showed that the neutrophil-mediated innate immune response damages neuroepithelial cells.[18] Another study found IL-6 to be significantly elevated in plasma, saliva and nasal mucosa in patients with hyposmia. IL-6 is a known proinflammatory cytokine that is present in other chronic diseases.[19] Although there is much work to be done to elucidate the contributions of the immune response, there appears to be a correlation between the immune response and PVOD.

Ultimately, more studies need to be done to identify the exact underlying mechanisms of chronic olfactory dysfunction following viral infections, and whether this is consistent or varies

depending upon the infecting virus. The complexity of olfaction allows for many possible pathways. Nonetheless, current data suggests that the changes to the neuroepithelium and olfactory bulb may be the key areas in the pathophysiology of post-infectious olfactory dysfunction.

Table VII.5 Section Evidence Summary Table: Non-COVID-19 Post-Viral Olfactory Dysfunction

Study	Year	LOE (1-5)	Study Design	Study Groups	Clinical End Point	Conclusion
Rombaux et al.	2009	4	Retrospective Cohort	1) 122 patients undergoing psychosocial and electrophysiologic recordings after chemosensory stimuli 2) 50 patients underwent imaging for olfactory bulb measurements	1) Sniffin' sticks test 2) Electrophysiologic responses 3) MRI measurements of olfactory bulb	1) Hyposmia was more prevalent than anosmia. 2) 35 showed olfactory event-related potentials. 109 had trigeminal event-related potentials. 3) Greater decrease in olfactory bulb size correlated with greater lost of smell.
Kattar et al.	2020	1	Systematic Review	N/A	N/A	Olfactory training demonstrates clinically significant improvement in post-viral olfactory dysfunction
Cavazzana et al.	2018	3	Retrospective Cohort	791 patients underwent Sniffin' Sticks test at first and final visits	1) Threshold, discrimination, and identification (TDI) scores	46% of anosmic patients and 35% of hyposmic patients had clinically significant improvement in smell over an average of 1.94 years.
Lee et al.	2020	1	Systematic Review	N/A	N/A	Post-viral olfactory dysfunction is complex with many possible mechanisms.
Suzuki et al.	2007	4	Cross-sectional study	24 patients with PIOD	1) Identification of virus present in a patient with olfactory dysfunction	1) Rhinovirus in 10 patients. Coronavirus in 1 patient. Parainfluenza in 1 patient. EBV in 3 patients.
Wang et al.	2009	4	Case-Control study	1) 25 patients with PVOD 2) 22 controls	1) Identification of PIV3	22/25 patients had positive PIV3 epithelial samples compared to 2/22 positive PIV3 epithelial samples.
Tian et al.	2021	4	Cross-sectional study	151 patients with PVOD were enrolled with samples taken from 38 patients who visited within 3 months of symptom onset.	1) Sniffin' Sticks test to evaluate olfactory function 2) Detection of viruses in olfactory cleft specimens	Rhinovirus detected in 13/38 patients. Coronavirus OC43 detected in 1/38 patients.

Jafek et al.	2002	4	Cross-sectional study	1) Unknown number of patient samples.	Histopathologic slides of nasal epithelium biopsies	Replacement of the neuroepithelium with respiratory-like epithelium, a highly disorganized olfactory epithelium, and metaplastic squamous epithelium
Mueller et al.	2005	4	Case-Control study	1) 22 patients had post-URI olfactory deficits 2) 9 patients had post-traumatic olfactory deficit. 3) 17 healthy controls	1) Sniffin' sticks test 2) MRI using CISS-Sequence	Presence of smell dysfunction is associated with reduced olfactory bulb volumes
Yao et al.	2018	4	Case-control study	1) 19 controls 2) 19 cases	Volumetric measurements of the olfactory bulb	Decrease in size of olfactory bulb is negatively correlated with duration of olfactory loss. A secondary outcome showed decrease of the right olfactory cortex in the case group.
Chung et al.	2018	4	Retrospective Cohort	34 patients with subjective olfactory dysfunction	1) Sniffin' Sticks test 2) MRI of olfactory bulb	10 patients were normosmic. Those who were hyposmic/anosmic o n the Sniffin' Sticks test had a higher detection rate of olfactory bulb atrophy.
Henkin et al.	2013	3	Case-control study	1) 59 patients (26 men and 33 women) who had varying degrees of smell loss. 2) 9 controls (5 men and 4 women)	1) Olfactory function measured by detection thresholds and recognition thresholds. 2) Plasma sample 3) Urine sample 4) Parotid saliva sample 5) Nasal mucus sample	Plasma levels of IL-6 were significantly elevated in patients with olfactory dysfunction compared to the controls.

- **Olfactory Dysfunction Can Occur after Viral Infection**
  Aggregate Grade of Evidence: C (Level 2b: 2 studies, Level 3c: 2 studies, Level 4c: 8 studies

SECTION: VII. Pathophysiology

B. Post-Viral Loss

2) COVID-19 related

Otolaryngologists were the first to draw attention to COVID-19 related smell loss, and champion it's role as an early, and often only, sign of COVID-19 infection.[1-3] Despite the rapidly growing evidence base, the exact mechanisms underpinning the pathophysiologic basis for olfactory dysfunction related to this viral process are still under investigation, and our understanding is likely to continue to evolve as evidence accrues. Three mechanisms have been proposed and likely co-exist; conductive loss due to olfactory cleft obstruction, injury to the olfactory epithelium, and injury to the olfactory bulb.

Conductive anosmia

Impairment of nasal airflow due to nasal obstruction will restrict delivery of odorants to the olfactory epithelium, a common cause of short term olfactory impairment associated with the "common cold" caused by endemic coronaviruses.[4,5] However, although nasal congestion is sometimes reported by patients with COVID-19, it is less frequently reported than with other coronavirus associated upper respiratory infections,[7] suggesting an alternative or additional mechanism may be responsible.

Nevertheless, localized obstruction caused by edema within the olfactory cleft has been proposed as one potential mechanism, and one study has shown a high prevalence of complete obstruction of the olfactory cleft in MRI scans performed within 15 days of onset of COVID-19 OD,[7] which had resolved in more than half at one month follow-up, accompanied by improvement in olfactory function. In contrast, other radiological studies of patients with more persistent loss have found this to be an uncommon persistent finding.[8] Whether obstruction of the OC contributes to the severity of early OD by preventing access of odorants to the OSNs, or reflects a consequence of epithelial injury is unclear at this time.

Injury to the olfactory epithelium

Olfactory epithelial injury has been demonstrated in prior cases of post-viral loss, and could account for the transient edema noted in the olfactory cleft discussed above. Histological studies in prior non-COVID-19 cases of post-viral loss have demonstrated damage to the

olfactory epithelium including OSNs and consequent scarring and atrophy, with correlation found between the severity of epithelial destruction and olfactory dysfunction.[9] A post-mortem study of 2 COVID-19 patients reporting anosmia showed focal atrophy of the olfactory epithelium, leukocytic infiltration of the lamina propria and evidence of axonal damage in the olfactory nerve fibres.[10] Similarly, animal models of SARS-CoV-2[11] have demonstrated massive destruction of the olfactory epithelium after nasal inoculation and loss of cilia, with evidence of recovery observed as early as day 4 after exposure though incomplete by day 14.

Angiotensin Converting Enzyme 2 (ACE2), a receptor on the cell surface required for SARS-CoV-2 viral entry, has been shown to be expressed by the sustentacular supporting cells and basal cells of the olfactory epithelium (OE), but not on the olfactory sensory neurons (OSNs) themselves.[12,13] Staining from a pre-clinical study showed that SARS-CoV-2 infected the sustentacular cells but not OSNs, and the virus was not found in the olfactory bulb or CNS.[14] The sustentacular cells support ORN function in a number of ways, including endocytosing odorant-binding proteins, removing toxic volatiles and by supplying glucose to the cilia of the ORN. Therefore damage to these cells may precipitate reduced sensitivity and the loss of cilia from the OSNs, resulting in olfactory dysfunction even though the OSNs do not themselves express ACE2 or become directly infected. Injury to the supporting cells as the predominant mechanism causing OD seems consistent with the rapid pattern of recovery reported in the majority of patients, with many reporting resolution within the first 7-14 days,[15–17] faster than would be expected for immediate OSN replacement and maturation but in keeping with the faster recovery of sustentacular cells.[18] In more severe cases, loss of the supporting cells could lead to an eventual secondary loss of the OSNs, as their role in supporting the normal inherent regenerative turnover of OSNs is in keeping with the presentation of many of these patients with initial recovery from their COVID-19 related loss who then present 3-4 months later with a secondary hyposmia, often accompanied by parosmia.

In addition, the immune response may be playing a role in COVID-19 related OD. Large increases in macrophages are found in the OE and lamina propria of animal models after SARS-CoV-2 infection.[12] Persistence of inflammation may prevent recovery of the olfactory epithelium and restoration of the OSNs. Induction of inflammation in a murine model of chronic

rhinosinusitis associated anosmia demonstrated inhibition of basal cell differentiation and neuronal depletion.[19] Olfactory epithelial biopsies from 3 deceased COVID-19 patients had significantly higher levels of the pro-inflammatory cytokine TNF-alpha than biopsies taken from non-infected living controls[20], although post-mortem artifact cannot be excluded. Some of the most recent studies, available currently only in preprint and therefore to be interpreted with caution, propose an inflammatory-mediated loss of odorant receptor expression on otherwise intact OSNs; this is supported by animal models,[21] and in olfactory epithelial biopsies harvested from COVID-19 patients post-mortem.[22]

Clinical studies have found that the severity of olfactory dysfunction is inversely correlated to recovery rates,[15,16] and may also reflect the severity of epithelial injury. An *in vivo* biopsy of a patient with anosmia persisting 3 months after diagnosis showed extensive destruction of the olfactory epithelium consistent with mucosal biopsies harvested early in the course of infection in animal models.[23]

Olfactory bulb infection and propagation to the CNS

Propagation of viruses by retrograde axonal transport to the olfactory bulb (OB) and beyond to the CNS is well described,[24] and has been shown to be associated with anosmia in herpetic encephalitis[25] in murine models. Animal models of OC43 coronavirus infection have demonstrated viral particles within the olfactory bulb 3 days after inoculation,[26] and through the cortex by day 7. ACE2 transgenic mice inoculated with SARS-CoV-1 similarly supported a route of viral entry through the OB with rapid invasion of the CNS.[27]

A series of 37 MRI scans performed in hospitalized patients with COVID-19 reported signal abnormalities of the OB in 19% of cases.[28] Several case reports documented hyperintensity in the olfactory bulb which resolved on repeat imaging one month later with subsequent loss of volume of the OB[29–31]; however it was unclear if this reflected transient initial edema or subsequent atrophy. Patients with post-viral olfactory loss have previously been found to have reduced volume in the OB and olfactory cortex.[32] One patient with persistent COVID-19 induced OD had MRI imaging prior to COVID-19 infection which provided baseline volumes of her OB, and confirmed significant atrophy of the OB in images performed 2

months after onset.[33] PET imaging found hypometabolism in the gyrus rectus in 2 patients with persistent COVID-19 OD.[34] While these studies have reported evidence of neurotropism, atrophy and hypometabolism , this may be an indirect consequence of loss of function at the level of the olfactory epithelium, and they do not provide direct proof of retrograde transport of SARS-CoV-2 into the OB.

One of the first post-mortem studies in a patient with severe respiratory COVID-19 disease and anosmia found extensive tissue damage within the olfactory nerve and intracytoplasmic viral inclusion bodies in the OB.[35] A larger post-mortem series in pre-print demonstrated that 3 out of 32 olfactory bulb samples were positive for SARS-CoV-2 RNA.[36] In contrast a series of 4 post-mortem studies failed to demonstrate injury to either the OE or OB, although it was not reported if these patients reported olfactory deficits.[37]

We are slowly gaining better understanding of how SARS-CoV-2 gains entry into the OSNs and the olfactory bulb in the absence of ACE2 expression. SARS-CoV-2 may utilize basigin (BSG; CD147) and neuropilin-1 (NRP1) as docking receptors on intracerebral vascular endothelial cells in order to cross the blood brain barrier (BBB), while a range of proteases including TMPRSS11A/B, cathepsin B and L, and furin (*FURIN*) have been shown to facilitate viral cell entry and replication.[38] Alternatively, the virus may gain entry through CSF filled spaces in perineural nerve sheaths and then into the ventricular system.[39]

Anosmia as a protective mechanism?

The destruction of the olfactory epithelium is thought to be an unwanted consequence of direct infection of epithelial cells and injury caused by associated inflammation. The prevalence of olfactory loss appears to be higher in patients reporting a milder course of COVID-19 infection.[40,41] Although this may simply reflect recall bias in patients with more severe symptoms,[42] one study utilizing psychophysical testing found a higher prevalence of OD 30 days after infection in patients with mild or moderate disease when compared with those with severe COVID-19.[43] It has been hypothesized that the damage to the olfactory pathway may be protective in preventing viral entry to the CNS.[44] There is some support from animal models for this theory; destruction of the olfactory epithelium prior to inoculation has been shown to

protect against intracranial invasion in murine studies.[24] Similarly ablation of the OB can prevent CNS infection after nasal inoculation with a neurotropic coronavirus.[45]

It is possible that post-COVID olfactory dysfunction may be caused by disruption at many levels of the olfactory pathway, however current evidence supports viral mediated injury to the sustentacular cells, resulting in indirect injury to the OSNs or down regulation of receptors as the most likely mechanism in COVID-19 related anosmia. While recovery may occur quickly in most patients, ongoing disruption of the OE or persistent inflammation may account for more long-lasting loss. There is less evidence to support a neurotropic pathway as playing a major role. The mechanism underlying parosmia, a prevalent symptom developing in the months after SARS-CoV-2 infection, is likely intimately related to the underlying mechanism of olfactory loss, and is an area where further research is needed.

SECTION: VII. Pathophysiology

C. Head trauma

Olfactory impairment associated with traumatic injury (head trauma or brain injury) can be attributed to several mechanisms: 1. Injury to the nasal cavity resulting in a conductive loss (blockage of airflow to the olfactory receptors), 2. Injury to the olfactory nerves preventing olfactory signals from reaching cortical regions for odor processing (discrimination, identification),and 3. Brain injuries including cortical contusion and hemorrhage resulting from coup or contrecoup injuries, or displacement of the brain within the cranial vault. In moderate to severe head injuries, severing of the olfactory nerves at the level of the cribriform plate may result in a total loss of smell function (complete anosmia).

Head injury is one of the most common causes of posttraumatic olfactory loss. In a US national study of 1,281 adults, olfactory function was found to be impaired in those 40 years and above in 10.1 percent who reported loss of consciousness due to head injury (n=178) and 10.0% of those reporting serious injury to the face or skull (n=203).[1] In a study of 114 children with head injuries, olfactory impairment was present in 12% of the cases.[2] Multiple studies have examined the overall occurrence of olfactory impairment following head injury with reports ranging between 7 and 22%.[1,3–7]

Trauma to the nasal passages and conductive pathways can block airflow and impair olfactory function. Biopsy of patients with trauma related anosmia have revealed injury to the olfactory receptor cells and cilia.[8] Fractures including fronto-orbital and Le Fort fractures have been associated with posttraumatic smell loss. In a study of 5,000 patients with injuries to the head or face,[9] olfactory impairment was found in 44.8% of those with facial or skull fractures and 11.3% of those with fractures of the nasal bones.

A common sequela of head injury is damage to the olfactory nerves, even in mild cases of head injury.[10] Back and forth movement of the brain (Coup-contra-coup forces) generated in blows to the head can tear or cause injury to the delicate olfactory nerve fibers as they pass through the cribriform plate and connect with the olfactory bulbs.[11,12]

Cortical injuries resulting from head trauma, including contusions and bleeding, may result in anosmia, hyposmia, parosmia or phantosmia. The type of smell loss depends upon the brain regions involved.[13] Yousem et al[14] studied primary sites of injury in patients with posttraumatic anosmia and hyposmia. Using MRI they found the highest incidence of posttraumatic encephalomalacia was in the olfactory bulb and tracts, subfrontal lobes, and temporal lobes. In a study of 176 combat blast injuries, 35% of those with olfactory loss had abnormal brain imaging.[15] Skull base fractures are likely to injure the olfactory nerves and result in complete anosmia.[4] Blows to the back of the head are more likely to result in olfactory loss than blows to the front.[9,16,17] Sports injuries also play a role in olfactory loss. In a study comparing American Football (AF) players and controls, 17 % of the football players had olfactory losses attributed to either a single traumatic brain injury (TBI), or multiple TBIs.[18] Olfactory loss increases with severity of injury, defined by posttraumatic amnesia (PTA),[17] Glasgow Coma Scale (GCS), or mild, moderate or severe head injury.[5,19,20] Children with mild head trauma were found to have lower olfactory function scores than an age matched control group.[21] Lower GCS scores in children also correlate with poor performance on olfactory tests.[22]

Table VII.6. Section Evidence Summary Table: Related to Head Trauma

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Hoffman et al[1]	2016	4	Cross-sectional national health survey	1. Responders reporting head injury with loss of consciousness (LOC)((n=178) 2. Responders reporting serious injury to the face and/or skull (n=203)	-Subjective smell loss + -Forced choice 8-item smell identification test	In responders aged 40 yo and above: 10.1% of those with head injury and LOC had smell loss 10.0% of those with facial or skull base injury had smell loss
Schreiver et al[2]	2020	4	Case series	Pediatric patients seen in a smell and taste clinic (n=164)	Sniffin' Sticks olfactory test	Headd trauma was the etiology of smell loss in 12% of these patients with olfactory dysfunction (OD)
Costanzo et al[3]	1986	4	Case series	Patients with head trauma	Not specified	Olfactory impairment occurs in 23.6% and 26.6% of motor vehicle accidents and domestic falls, respectively
Ogawa et al[4]	1999	4	Cross-sectional survey	Occupationally head-injured workers (n=365)	Psychophysical smell testing	13.7% of occupationally head injured workers had smell impairment This was associated with LOC, more

						severe injuries, and skull fracture.
Singh et al[5]	2018	4	Case series	Patients with Traumatic Brain Injury (TBI) (n=774)	Olfactory function assessed via sensitivity to coffee granules	19.7% of patients with TBI had olfactory impairment This was associated with increased severity of TBI and co-morbid medical illnesses
Sumner[6]	1964	4	Case series	Patients presenting with a wide variety. Of head injuries, from minor to more severe (n=1,167)	Subjective smell loss	7.5% of all head injury patients experienced olfactory impairment 39% experienced some recovery
Temmel et al[7]	2002	4	Case series	Patients with anosmia or hyposmia (n=278)	Sniffin' Sticks olfactory test	17% of patient.s with olfactory loss had trauma as an etiology
Zusho[9]	1982	4	Case series	Patients with head trauma (n=5000)	"Standard olfactory acuity test"	4.2% (n=212) of the 5000 head trauma patients had olfactory impairment Of these 212 patients, 72.6% had anosmia while 27.4% had hyposmia Olfactory impairment was found in 44.8% of

						those with facial or skull fractures and 11.3% of simple nasal fractures.
Xydakis et al[15]	2015	3	Cohort study	Soldiers with acute TBI severe enough to be transferred stateside and evaluated directly off the battlefield with and without olfactory. impairment	UPSIT MRI	Abnormal olfaction predicted internal brain injury, with normal or mild TBI patients scoring within the normosmia range. Patients who had frontal lobe injury were 3 times more likely to have olfactory impairment than those with injuries in other regions.
Querzola et al[18]	2019	4	Case-control study	American football (AF) players (n=75) and normal controls (n=30)	Tra-Q (Trauma Questionnaire) includes subjective smell questions	17% of AF players had olfactory impairment related to one or multiple TBIs
Schriever et al[21]	2014	4	Case-control study	Pediatric patients with mild head trauma (n=114) and normal controls (n=56)	Modified Sniffin' Sticks olfactory test	Pediatric patients with mild TBI had significantly worsened. TDI scores compared to controls, but they still fell within the normal range.

- **Olfactory Dysfunction can be Caused by Head Trauma**

Aggregate Grade of Evidence: C (Level 3: 1 study, Level 4: 10 studies)

SECTION: VII. Pathophysiology

D. Related to toxin exposure, environmental or work-related

The true prevalence of olfactory impairment related to occupational exposure to chemicals is unknown with a likely frequency of 0.5 to 5% of all olfactory dysfunction.[1] There is high likelihood that occupational exposure is underdiagnosed for patients presenting with idiopathic smell disorders.[1] Agents that have been associated with olfactory dysfunction include metals (cadmium, manganese, chromium, arsenic, lead, mercury, aluminum, nickel), organic compounds (butyl acetate, benzene, benzyl acetate), industrial agents (paint solvents, styrene, toluene), dusts (cement, hardwood) and nonmetal inorganic compounds (methylbromide, hydrogen sulfide, chlorine).[2]

Metal exposure occurs in the form of metal dust or vapors.[3] Of the metals, cadmium is the most commonly known to cause olfactory impairment, as this metal targets the first olfactory neuron.[2,4] Cadmium is used in the production of storage batteries and can be present in the environment through waste incineration, sewage, and fertilizers.[5] Previous studies have found a higher prevalence of smell loss and higher olfactory thresholds in cadmium exposed workers compared to controls, which is directly related with the years of exposure.[4,6–11,12]

Exposure to manganese, another metal, is also associated with olfactory dysfunction.[13–17] Inhaled manganese is absorbed by the olfactory neurons and transported from the olfactory bulb to the olfactory cortex.[18] In manganese exposed ferroalloy plant workers, high urinary manganese was associated with worsened odor detection thresholds.[17] However, in professional welders exposed to manganese, workers with the highest manganese blood levels exhibited better olfactory function than those with the lowest levels.[8] Whether this effect is transitory before decompensation of the olfactory function, is unknown.[15]

Styrene is a solvent used in the plastic industry that has been associated with atrophy of the olfactory epithelium in mice.[19] However, in humans, a study of chronically exposed workers to styrene, there were no differences in the phenylethyl alcohol detection threshold and odor identification compared to controls.[20] Interestingly, the exposed workers did have exposure-

induced olfactory adaptation with elevated thresholds to the exposed odor which is known as "industrial anosmia".

A variety of industrial solvents and solvent mixtures which contain hydrocarbons have been associated with olfactory impairment. Hydrocarbons can be present in cleaning products, paints, and in printing and plastic manufacturing, among other products.[21–26] In a cross-sectional study, respondents with exposure to vapors such as paints, cleaning products, glues, solvents, acids, or welding/soldering fumes were more likely to have experienced olfactory disturbance in the last 12 months.[15] In previous studies, workers of plastic manufacturing had decreased olfactory threshold scores but not in their odor identification scores.[27] In a cross-sectional study of Korean workers in automobile repair, printing, shoemaking and plating industries, all had higher prevalence of olfactory dysfunction compared to office workers.[28]

Ambient air pollution may also impact olfactory function by contacting the olfactory epithelium, translocating to the olfactory bulb and migrating to the olfactory cortex causing direct damage of the tissue or inducing local inflammation.[29] In older U.S. adults, exposure to nitrogen dioxide was associated with olfactory dysfunction.[30] Residents of cities exposed to severe air pollution have olfactory dysfunction demonstrated by worse smell scores than those living in non-polluted regions. Moreover, the olfactory bulb showed endothelial hyperplasia and neuronal accumulation of particles.[31]

The available evidence shows that association of multiple environmental, toxin and work factors are related to olfaction impairment, however, no direct causality can be concluded.

Table VII.7. Section Evidence Summary Table: Related to Environmental or Work-related Toxins

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Adams et al[6]	1961	4	Case-control	1)106 alkaline battery workers exposed to cadmium and nickel dust	1) Subjective assessment of sense of smell (good, diminished, none)	Workers had 15% anosmia, compared to controls with 0%

				2)84 Controls	2) Phenol smell testing	Workers performed more poorly on phenol testing (27.3 vs 4.8%). Anosmia is due to exposure to cadmium, nickel, or a mixture of both.
Potts et al[7]	1965	4	Cross-sectional	1)70 alkaline battery workers	1) Percentage of anosmia	65% anosmia in 10-19 years of exposure, 53% in 20-29 years of exposure and 91% in 30-40 years of exposure.
Ishinini et al[32]	1977	4	Descriptive	1)Retired workers of arsenic mine		9 of 21 roasters who often worked in the kitchen had dermatitis, depigmentation, septum perforation, hyposmia, anosmia, peripheral nerve disturbance.
Ahlstrom et al[21]	1986	4	Cross-sectional	1)20 tank cleaners exposed to petroleum 2)Controls (office workers and watchmen)	1)Odor detection thresholds and perceived odor intensity of 4 stimuli	Tank cleaners had higher absolute odor threshold and normal perception of strong stimuli but impaired for weak stimuli.
Sandmark et al[22]	1989	4	Cross-sectional	1)54 painters exposed to organic solvents 2)42 unexposed controls	1)UPSIT	The painters had lower score but in multiple regression analysis the influence of exposure was not statistically significant. The exposure was low, an effect for high exposure cannot be ruled out.

Schwartz et al[26]	1990	4	Cross-sectional	1)187 workers in paint manufacturing	1)UPSIT	Dose-related decrements in olfactory function only in non-smokers.
Hotz et al[24]	1992	4	Cross-sectional	1)264 workers exposed to hydrocarbons 2)Controls	1)memory index 2)subjective smell/taste impairment	8.8% workers with disturbance of smell and taste vs 1.3% of controls.
Rose et al[12]	1992	4	Cross-sectional	1)55 workers with chronic exposure to cadmium fumes in a brazing operation 2) Control group	1) urinary cadmium levels 2)cadmium induced renal damage 3)olfactory function through butanol detection threshold and odor identification	Of workers:40% mildly hyposmic, 13% moderately or severely hyposmic Reference group: 31% mildly hyposmic Patients with renal damage had more significant olfactory dysfunction.
Mergler et al[25]	1992	4	Cohort	1) 5 healthy subjects exposed toluene and or xylene	1)Olfactory perception threshold	6-fold increase of threshold that returned to normal at a rate of 6.8ds/hr.
Wieslander et al[23]	1994	4	Cross-sectional	1)255 painters (solvent based paint) 2)302 exposed to water-based paint	1)Self-administered questionnaire to assess occurrence of symptoms	Taste or olfactory disturbances 3% in workers with solvent based paint vs 0.4% in workers with water-based paint.
Mergler et al[16]	1994	4	Case-control	1)115 workers employed in manganese alloy production 2)matched controls	1)Emotional state 2)Motor functions 3)Cognitive flexibility 4)Olfactory perception threshold for PM-Carbinol	Manganese workers had significantly worsened smell thresholds compared to their matched pairs. Pairs differed on emotional state, motor function, cognitive flexibility, and olfactory perception. No

					5)basic mathematics 6)Reading capability 7)Attentional capacity	difference was found in verbal fluency, mathematics, reading and attentional capacity.
Lucchini et al[17]	1997	4	Cross-sectional	1)35 male workers of a ferroalloy production plant exposed to manganese oxides 2)Control group of not exposed workers	1)Psychomotor function scores 2)Olfactory threshold 3)White blood cell counts	The olfactory threshold did not differ between the groups but was negatively associated with urine manganese suggesting that increased excretion is related to increased olfactory perception. Changes in leukocyte count may indicate affect on immunological system.
Rydzewski et al[10]	1998	4	Cross-sectional	73 workers exposed to cadmium in quantities exceeding maximum allowable concentration	Olfactometry was performed according to Elsberg and Levy's method, modified by Pruszewicz	Hyposmia had a prevalence of 26.0%, parosmia 17.8% and anosmia 1.4%. Correlation between olfaction impairment and cadmium concentration in blood, urine and workplace air.
Sulkowski et al[9]	2000	4	Case Control	1)73 workers of cadmium-nickel batteries plant 2)43 Controls	1)Threshold measurements (maximum and minimum)	Olfactory dysfunction on 45.2% of exposed and 4.6% of controls. Correlation found between blood/urine cadmium and olfactory dysfunction.
Schwartz et al[33]	2000	4	Longitudinal	1)535 former lead manufacturing workers	1) Neurocognitive tests 2)UPSIT	Significant decline in UPSIT score in former lead workers.

				2)118 controls		
Dalton et al[20]	2003	4	Cross-sectional	1)workers exposed to styrene in plastic industry 2)Controls	1)Threshold for phenylethyl alcohol 2)Odor identification 3)Retronasal odor perception	No difference in olfactory function. Exposed workers had elevated styrene odor detection threshold (induced adaptation).
Mascagni et al[4]	2003	4	Cross-sectional	1)33 workers in cadmium fusion 2)39 workers in reference group 1 not exposed 3)Reference group 2: 23 workers exposed to Iron and steel welding fumes	1) Olfactory threshold and odor identification ability 2) Blood and urinary cadmium values	Mean olfactory threshold was significantly worse in cadmium workers. The odor identification test findings for cadmium workers were similar to those of the reference groups.
Cheng et al[27]	2004	4	Cohort	1)52 Workers exposed to acrylonitrile-butadiene-styrene thermal decomposition products 2)Reference group not exposed (n= 72)	1) 1-butanol threshold 2)Odor identification, both pre- and post-work	Exposed group had lower olfactory function after work. Exposed workers had decreased olfactory threshold scores, but no difference in odor identification scores.
Hudson et al[34]	2006	4	Cross-sectional	82 Mexico City subjects (high air pollution)	Olfactory identification and threshold using	Mexico City residents performed worse except the 50 to 63 year old age

				86 Tlaxcala subjects (low air pollution)	an orange drink and coffee. Odor discrimination using horchata and atole beverage	group, in which there was no difference.
Antunes et al[8]	2007	4	Case-control	1)Professional welders (n=43) who worked 1 or 2 years on the SF/Oakland Bay bridge 2)Matched controls	1)UPSIT scores 2)Neurologic and neuropsychological test measures	Welders may be at risk for loss of smell function, unrelated to neurological and neuropsychological test performance.
Guarneros et al[35]	2009	4	Cross-sectional	1)30 Mexico City subjects (high air pollution) 2)30 Tlaxcala subjects	Sniffin' sticks odor identification, threshold and discrimination	Mexico City residents performed worse in threshold and discrimination but not in identification.
Ranft et al[36]	2009	4	Cross-sectional	399 women exposed to traffic related particulate matter	Sniffin' sticks odor identification	Motor vehicle exposure was associated with poorer olfaction.
Calderón-Garcidueñas et al[31]	2010	4	Case Control	Olfactory Bulb of: 1)35 residents of Mexico City exposed to severe air pollution 2)9 controls UPSIT scores of: 1) 62 residents of Mexico City 2)25 controls	1)UPSIT 2)Light and electron microscopy of the olfactory bulb	Cases had worse UPSIT scores and olfactory bulb pathology findings including endothelial hyperplasia, neuronal accumulation of particles.

Lucchini et al[13]	2012	4	Cross-sectional	Adolescents 11-14 years residing in Valcamonica, (region impacted by ferroalloy plant emissions containing manganese and other metals for a century) or a Reference area. 1)Exposed area (n=154) 2)Reference area (n=157)	1)Motor coordination (Luria-Nebraska test) 2)Hand dexterity (Aiming pursuit test) 3)Odor identification (Sniffin' Sticks task) 4)Tremor intensity	Exposure to manganese was associated with deficits in olfactory and motor function.
Sorowska el al[37]	2013	4	Cross-sectional	1)151 native Amazonians 2)286 subjects living in Dresden	Olfactory threshold with Sniffin' sticks	Dresden (higher air pollution) residents performed worse.
Grashow et al[38]	2015	4	Cross-sectional	165 men from the Normative aging study who previously had bone lead measurements	1)UPSIT score 2)Global cognition (mini mental exam) 3)cumulative lead exposure	Cumulative exposure to lead is associated with reduced olfactory recognition. This was attenuated in men with better cognitive function.
Adams et al[30]	2016	4	Cross-sectional	Respondents from the National Social Life, Health, and Aging Project	Validated odor identification test	Increase in nitric dioxide exposure was associated with increased odds of olfactory dysfunction.
Riccó et al[39]	2016	4	Cross-sectional	66 workers exposed to phenolic resins	1)Self-reported olfactory impairment (hyposmia, anosmia,	31.8% hyposmia, 18.2% anosmia and 13.6% hyperosmia. High exposure to phenol was the main risk factor for anosmia.

					hyperosmia)	Exposure to phenol may be associated with self-reported olfactory impairment.
Noel et al[15]	2017	4	Cross-sectional population-based study of the 2011-2012 and 2013-2014 National Health Examination and Nutrition Survey	3594 respondents from 2011 to 2012 and 3708 respondents from 2013 to 2014	1) Frequency of self-reported smell disorders 2) Performance on odor identification testing (8-item odor identification test Pocket Smell Test, Sensonics, Inc., Haddon Heights, NJ).	Exposure to vapors, urinary levels of manganese, 2-Thioxothiazolidine-4-carboxylic acid, 2-Aminothiazoline-4-carboxylic acid, 2,4 dichlorophenol, and serum lead levels were all implicated in smell disturbance.
Lee et al[28]	2018	4	Cross-sectional	1) Exposed group (n=296) workers in the automobile repair, printing, shoemaking and plating industries 2)Office workers, non-exposed group, n=99	1)Olfactory function was evaluated using the Korean version of Sniffin' Sticks	In comparison with office workers, the prevalence of olfactory dysfunction was higher in the four occupational groups.
UPSIT: University of Pennsylvania Smell Identification Test.						

- **Toxin exposure, environmental pollution, and exposure to particulate matter is associated with smell disorders.**

  Aggregate grade of evidence: C (Level 4: 30 studies).

SECTION: VII. Pathophysiology

E. Related to medications

Numerous medications from a broad range of therapeutic classes have been associated with changes in olfactory function. Despite the commonality of medication-related changes in olfaction, there is a paucity of research on both the implicated medications and underlying pathophysiology of olfactory dysfunction. The lack of such data is both due to the wide range of incidence of medication-related olfactory changes, and also because the patient population that most commonly experiences medication-related changes in olfaction often also has many risk factors for baseline olfactory dysfunction including advanced age, medical comorbidities, and polypharmacy.[1,2] Additionally, the complexity of the olfactory system further complicates this mechanistic investigation, as many of the hundreds of receptors and interacting molecular signaling pathways that make up the olfactory system are potential targets of an exponential amount of indiscriminate drug interactions.[3]

The body of literature dedicated to medication-related changes in olfaction is of low quality and summarized in **Table VII.8**. Though many reports of olfactory loss following administration of medications are anecdotally described in large pharmaceutical databases,[4] there is increasing use of psychophysical olfactory testing used to describe the perturbations in olfaction. The drugs with the strongest data supporting associations of decreased olfaction include zinc, tetrahydrocannabinol (THC), remifentanil and sildenafil.[5–7] Furthermore, it has long been recognized that chemotherapeutic agents may also impair the regenerative ability of the olfactory system, leading to transient or more lasting effects.[1,8] Numerous other drugs are associated with reports of olfactory dysfunction, and include commonplace medications such as propofol, duloxetine, midodrine, metoprolol, local anesthetics, and oral antibiotics.[2,9–15] Meanwhile, there is some evidence that thyroid hormone modulation and α_{1A} adrenoceptor antagonism may lead to olfactory improvements, though the clinical significance and mechanism of these findings are unknown.[16]

Although several studies have investigated the use of oral zinc supplementation to treat olfactory loss without overall convincing evidence that it can,[17] it has been widely recognized

that topical administration of zinc ions is associated with olfactory loss. Initially, during the 1930s, it was demonstrated that topical administration of zinc sulfate could result in olfactory dysfunction, and then approximately 70 years later the topical administration of zinc gluconate was found to have similar effects.[18–22] In vitro animal studies suggest that topical administration of zinc contributes to cell death of olfactory neurons and direct loss of the olfactory neuroepithelium.[23,24]

Although the quality of evidence for each individual medication is of low quality and pathophysiologic mechanisms are poorly understood, there is substantial evidence that medication usage of a wide array of both prescription and non-prescription medications may result in deficits of olfactory function. Importantly, for otolarynngologists who routinely use topical tetracaine, lidocaine and phenylephrine in their offices, although tetracaine and lidocaine do cause a transient increase in olfactory threshold during the visit, these medications appear safe and without long term effect on the olfactory system.[13,14,15]

Table VII.7. Section Evidence Summary Table: Related to Medications

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Walter et al[5]	2014	2	Randomized placebo-controlled crossover study	Healthy subjects (n=15) 1) Placebo 2) 20mg oral THC	Psychometric orthonasal testing using Sniffin' Sticks at baseline and 2 hours after THC administration	THC was associated with increased threshold and reduced discrimination scores
Gudziol et al[7]	2006	2	Double-blind, placebo-controlled crossover study	Healthy subjects (n=20) following PO administration of: 1) 50mg sildenafil	Psychometric orthonasal testing using Sniffin' Sticks	Reduced discrimination and increased threshold following administration of 100mg sildenafil compared to other groups

				2) 100mg sildenafil 3) Placebo		
Jung et al[14]	2011	2	Double-blind RCT	Healthy subjects (n=72) 1) Placebo 2) Phenylephrine 3) Lidocaine 4) Both agents	Korean version of Sniffin' Sticks test II at baseline and 15 min post-administration	No difference in TDI scores among groups
Lötsch et al[6]	2001	3	Randomized placebo-controlled	Healthy subjects (n=13) with plasma concentrations of remifentanil (0, 1.2, 1.8, 2.4, 3, 3.6, 4.8, and 6 ng/ml)	Psychometric orthonasal testing using Sniffin' Sticks at baseline and immediately after infusion completion	Increased threshold scores with increasing doses of remifentanil
Steinbach et al[8]	2009	3	Prospective cohort study	Chemotherapy for breast or gynecologic malignancy (n=87)	Psychometric testing using Sniffin' Sticks before, during, directly after and 3 months following chemotherapy	Chemotherapy has a transient effect on olfactory function. TDI was significantly impaired during therapy with near complete recovery at 3 months. Older patients were more affected than younger patients.
Alexander et al[20]	2006	4	Retrospective case series	Anosmia after intranasal zinc usage (n=17)	1) Threshold testing with butanol 2) Identification testing with 7 common odorants and 1 odorant to test trigeminal	Impaired threshold and identification in all patients. Intranasal zinc induced anosmia syndrome can be distinguished from post-

					function 3) UPSIT (for 9 pts) 4) Clinical history	viral anosmia based on history.
Davidson et al[21]	2010	4	Retrospective case series, causality analysis	Anosmia after intranasal zinc usage (n=25)	Bradford Hill 9 criteria	Clinical, biological, and experimental data support Bradford Hill criteria to show intranasal zinc gluconate causes dysomia
Hari et al[15]	2018	4	Prospective case series	Healthy subjects (n=6) given topical spray of 4% lidocaine	Threshold testing using amyl acetate	Transient increase in olfactory threshold that could be overcome by increased stimulus and return to normal threshold within 30 minutes
Welge-Lüssen et al[13]	2004	4	Prospective case series	Healthy subjects (n=20) given 1% tetracaine at 3 different locations and then 4% lidocaine in olfactory cleft	1) Self-assessment 2) Psychometric testing using Sniffin' Sticks 3) Olfactory event-related potentials	1% tetracaine was capable of inducing transient hyposmia but only 4% lidocaine applied directly to olfactory cleft could cause transient anosmia
Jafek et al[19]	2004	4	Case series	Patients with intranasal zinc gluconate-associated olfactory disturbance (n=10)	Clinical history	Intranasal zinc gluconate is associated with severe hyposmia with parosmia or anosmia
Du et al[9]	2018	4	Case report, literature review	1) Propofol as sole anesthetic 2) 6 case	1) Clinical history 2) Negative CT/ MRI	Propofol (and other anesthetics) may cause dysosmia, however the

				reports, dysosmia with varying anesthetics		mechanism is unknown
Yoshida et al[10]	2017	4	Case report	Duloxetine 20mg (n=1)	Threshold and identification using T&T olfactometer initially and then 7 days after cessation of duloxetine	Duloxetine may cause worsened threshold and identification levels which improve upon cessation of medication
Horger et al[11]	2016	5	Case report	Midodrine 5mg TID (n=1)	Clinical History	Self-reported dysosmia that improved upon cessation of medication
Che et al[12]	2018	5	Case report	Metoprolol (n=1)	Clinical History	Self-reported dysosmia that improved upon cessation of medication
Abbreviations: THC = Δ^9-tetrahydrocannabinol; TDI=Threshold, discrimination and identification; UPSIT=University of Pennsylvania Smell Identification Test						

- **Multiple medications can have detrimental effects on olfaction.**
  Aggregate Grade of Evidence: C (Level 2: 3 studies; Level 3: 2 studies; Level 4: 7 studies; Level 5: 2 studies)

SECTION: VII. Pathophysiology

F. Post-Radiation Therapy (RT)

Olfactory dysfunction (OD) is a potential sequela of radiation therapy (RT) for head and neck tumors, and various mechanisms of injury have been proposed. Several prospective cohort studies have demonstrated that patients treated with RT experience impaired olfaction during and immediately following completion of treatment, as measured by both subjective and objective metrics.[1–3] A systematic review of 23 studies demonstrated impairment in odor detection, discrimination, and identification after RT.[4] The majority of patients in these cohorts were treated for head and neck cancer, although some patients with brain tumors or cutaneous

malignancies have been studied as well. Following the completion of RT, some patients may experience a partial or even complete recovery of olfactory function.[1,2] In a study of 70 patients, Bramerson et al[4] demonstrated that radiation dose was significantly related to olfactory dysfunction, while age, sex, and concurrent chemotherapy administration were not.[4] In a series of 56 patients, Hölscher et al[3] demonstrated that higher radiation doses to the olfactory epithelium were associated with lower odor discrimination scores two weeks after initiating RT, but no dose-dependent difference was observed for odor identification and threshold scores.[3]

Several investigators have demonstrated persistent objective OD over one year following the completion of RT. Such studies have utilized a variety of outcome metrics, including the UPSIT, CCCRC, Sniffin' Sticks, and measurement of event-related potentials to assess odor thresholds, discrimination, and identification, suggesting that RT-induced OD is both qualitative and quantitative.[3–9]

Various mechanisms have been proposed regarding the pathophysiology of these observed changes, although there is limited evidence validating them. Proposed mechanisms include direct cytotoxic damage to the olfactory epithelium, olfactory bulb, or its supporting cells; impaired neurogenesis; treatment-induced obstruction of the olfactory cleft; and decreased vascular perfusion to the olfactory cleft. Murine models have demonstrated that ionizing radiation affects olfactory neurogenesis and olfactory bulb plasticity.[10,11] Patients with nasopharyngeal cancer treated with RT have been shown to exhibit reductions in olfactory bulb volume on post-treatment MRI, measured $\geq$1 year after completion of therapy.[9]

Regarding prognosis, there appears to be a radiation dose-dependent effect on long-term OD.[3,4,12] However, individual outcomes may be unpredictable, as Jilali et al[12] demonstrated that the actual dose delivered to the nasal mucosa and olfactory cleft is variable despite similar total radiation doses. This finding may explain some of the inconsistency in published outcomes of olfaction following RT.

Table VII.8. Section Evidence Summary Table: Related to Radiation Therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Álvarez-Camacho et al[7]	2017	2*	Systematic review	1) 23 studies 2) N range (13-1411 patients)	1) Olfactory dysfunction as a side effect of RT	Odor detection, identification, and discrimination are impaired after RT for HNC. A dose relationship exists between RT and odor identification and discrimination.
Brämerson et al[4]	2013	3	Cohort study	1) 14 patients with HNC whose treatment included high dose RT to the olfactory epithelium. 2) 56 patients with HNC whose treatment included RT sparingly the olfactory epithelium	1) Scandinavian odor identification test	20 months after RT, HNC patients treated with high doses to the olfactory epithelium had worsened odor thresholds and identification scores than those treated with low dose RT.
Galletti et al[8]	2016	4	Case control study	1) 9 patients with NPC treated with RT+chemotherapy	1) Olfactory event related potentials 2) Hyposmia Rating Scale 3) Olfactory VAS	Significant differences in the latency and amplitude of olfactory event-related potentials between patients and controls, correlating with subjective olfactory

				2) 9 healthy controls		assessments.
Gurusheka r et al[1]	2020	3	Cohort study	1) 13 patients with HNC undergoing RT	1) CCCRC test 2) Mucociliary clearance 3) AHSP questionnaire	Decrease in objective olfactory function during RT with improvement after 3 months, but persistent mucociliary dysfunction.
Hölscher et al[3]	2005	3	Cohort study	1) 22 patients undergoing H&N RT with high dose to olfactory epithelium 2) 22 patients undergoing H&N RT with low dose to olfactory epithelium	1) Odor identification 2) Odor discrimination 3) Odor threshold	During RT, no significant difference in odor threshold or identification between groups, but discrimination was significantly lower in those receiving a higher dose of RT. Odor identification was lower in patients with higher dose to olfactory epithelium $\geq$ 6 months post-RT.
Jalali et al[12]	2014	3	Cohort study	1) 54 patients with HNC or brain malignancy	1) Olfactory threshold 2) In vivo dosimetry	Reduced olfactory thresholds 6 months after RT, with a dose dependent response.
Riva et al[2]	2019	3	Cohort study	1) 10 patients undergoing RT for HNC, excluding nasal tumors.	1) Odor identification 2) Odor discrimination 3) Odor threshold	Decrease in odor threshold, discrimination, and identification during RT with recovery after 3 months. However, 40% with subjective persistent hyposmia.

					4) Nasal obstruction symptom score	
Riva et al[6]	2015	3	Cohort study	1) 30 healthy subjects 2) 30 patients with NPC treated with RT+chemotherapy	1) Odor identification 2) Odor discrimination 3) Odor threshold 4) Symptom survey	≥ 2 years post RT, patients exhibited worsened odor threshold and TDI scores as compared with healthy controls. No difference based on type of RT.
Veyseller et al[9]	2014	4	Case control study	1) 24 patients with NPC treated with RT ≥ 12 months ago 2) 14 healthy controls	1) CCCRC 2) Olfactory bulb volume (MRI)	Olfactory function and olfactory bulb size were significantly lower in patients following RT as compared to controls.
Wang et al[5]	2015	3	Cohort study	1) 41 patients with NPC treated with IMRT	1) UPSIT – TC 2) TWSNOT-22	One year after completion of IMRT, mild olfactory dysfunction still existed.

AHSP – Appetite, Hunger and Sensory perception

CCCRC – Connecticut Chemosensory Clinical Research Center

HNC – head and neck cancer

IMRT – intensity-modulated radiotherapy

NPC – nasopharyngeal carcinoma

Ref. – reference

RT – radiotherapy

TDI - threshold discrimination identification score

TWSNOT-22 – Taiwanese version of the 22-item Sino-Nasal Outcome Test

UPSIT – TC – University of Pennsylvania Smell Identification Test

VAS – visual analog scale

*LOE downgraded due to heterogeneity of results and lack of RCTs.

- **Radiation to the olfactory system can lead to olfactory dysfunction, that is sometimes temporary, but can be permanent in some patients.**

  Aggregate Grade of Evidence: C (Level 2: 1 study, Level 3: 7 studies, Level 4: 2 studies)

SECTION: IX. Pathophysiology

G. Related to underlying systemic disease

1) Auto-immune

Our systematic literature review identified that olfactory impairment is observed in many autoimmune diseases that have different underlying pathophysiology (**Table VII.9**). We identified studies in primary Sjogren Syndrome (pSS),[1–8] systemic sclerosis (SSc),[9,10] multiple sclerosis (MS),[11–38] granulomatosis with polyangiitis (GPA),[39–43] systemic lupus erythematosus (SLE),[10,44–46] rheumatoid arthritis (RA),[47] myasthenia gravis (MG),[48–50] neuromyelitis optica (NO),[51] Behçet's disease (BD),[52–54] and Mikulicz's disease (MD).[55] Studies have used different methodologies, but associations with age, sex,[5,16,22,28] and mood disorders[4,9,10,15,16] have been observed. Association with disease activity,[2,10,12,16,17,19,20,22–25,27,28,32–35,37,42,43,45,46,48,49] neurological manifestations,[10,12–18,20,22,25,27,28,32–35,37,38,44] magnetic resonance imaging (MRI) abnormalities,[10,13,18,21,25,26,30,36,51,54] and autoantibodies[10,48,51,52] have been observed in different autoimmune diseases. There are only 4 longitudinal studies, results regarding worsening or stabilization of olfactory dysfunction are therefore controversial.[10,32,35,37]

Table VII.9. Section Evidence Summary Table: Related to Autoimmune Disease							
Disease	**Study**	**Year**	**LOE (1 to 5)**	**Study Design**	**Study Groups**	**Clinical Endpoint**	**Conclusion**
Sjogren's syndrome (SS)	Al-Ezzi et al[1]	2017	2	Systematic review with meta-analysis	378 primary SS (pSS) patients. Compared to healthy controls	Standard mean deviation (SMD) of olfcactory ability from normal	The impact of pSS vs. healthy controls was: smell SMD 0.78 (95% CI 1.29 to 0.27)
	Henkin et al[2]	1972	4	Cross-Sectional study	29 patients SS/ 10 patients with various other diseases of the parotid glands	Detection and recognition thresholds for pyridine, nitrobenzene, thiophene	45% with hyposmia Cyclophosphamide improved smell function
	Jones et al[3]	1974	4	Case- control study	14 female patients with SS/ 16 controls	Forced choice three-stimulus sniff technique	All patient with SS had hyposmia, inflammatory changes in the nasal mucous membrane, and nasal accumulation of $^{99m}TcO_4$ in SS.

	Weiffenbach and Fox[4]	1993	4	Case- control study	30 patients SS/ 16 healthy controls (HC)	University of Pennsylvania Smell Identification Test (UPSIT)	Patients with SS scored worse than controls. The lower score of the patients showed a significant depression of olfactory sensitivity.
	Kamel et al[5]	2009	4	Case- control study	28 SS /37 HC	UPSIT	SS patient scored worse than controls. Taste and smell thresholds were correlated. Association with reduced quality of life
	Midilli et al[6]	2013	4	Case- control study	77 SS/ 77 HC	5 component smell discrimination test	SS patients scored the same as controls. Smell disorder was associated with nasal polyposis
	Su et al[7]	2015	4	Case- control study	15 SS/32 Burning Mouth Syndrome (BMS) patients used as controls	Sniffin' Sticks TDI	Olfactory scores were the same between SS and BMS groups
	Rasmussen et al[8]	1986	4	Case- control study	36 SS/36 controls	Elsberg`s olfactometer	No dfifference between groups. No correlation with mucociliary clearance

Systemic sclerosis (SSc)	Amital et al[9]	2014	4	Case- control study	20 SSc/ 21 controls	Sniffin' Sticks TDI	3 of 20 (15 %) SSc hyposmia TDI SSc < controls TDI scores correlate inversely with BDI-II
	Bombini et al[10]	2018	4	Case- control study	143 SLE and 57 SSc / 166 (HC)	Sniffin' Sticks TDI, MOCA, BAI, BDI, MRI, (anti-P) antibodies	Olfactory dysfunction 54.5% SLE, 59.3% SSc and 14.45% controls. SLE and SSc TDI< controls. Olfactory dysfunction was associated with age, inflammation and hippocampus and amygdala volume. In SLE association with anti-P, anxiety and depression symptoms.
Multiple sclerosis (MS)	Ansari et al[11]	1976	4	Case- control study	40 MS/24 controls	Amyl acetate and nitrobenzene were used in a double-blind test	MS patients have no detectable olfactory deficit compared with controls No correlation between visual and olfactory involvement

	Samkoff et al[12]	1996	4	Case- control study	16 MS/14 controls	UPSIT	MS patients scored the same as controls. Negative correlation between UPSIT scores and EDSS
	Doty et al[13]	1997	4	Case series	26 patients with MS	UPSIT, MRI with gadolinium	38.5% of MS with olfactory loss Negative correlation with lesion load
	Hawkes et al[14]	1997	4	Case- control study	72 MS/96 controls	UPSIT Olfactory evoked response (OEP)	15% patients had abnormal UPSIT. 25% patients had abnormal OEP UPSIT scores correlated with EDSS. UPSIT scores with the H2S-evoked response.
	Zivadinov et al[15]	1999	4	Case- control study	73 MS/40 controls	Cross-Cultural Smell Identification Test (CC-SIT) and clinical variables	12.5% MS patients had an absolute loss of smell. Borderline normal in 10% and abnormal in 12.5%. Correlations between the smell identification score and symptoms of

							anxiety, depression and severity of neurological impairment
	Zorzon et al[16]	2000	4	Case- control study	40 MS/40 control	CC-SIT	12.5% olfactory abnormal. CC-SIT MS score worse than control Sex, age, disease duration, disability, anxiety, depression, lesion load. Correlation between CCSIT score and olfactory brain lesion load, and negative correlation EDSS.
	Fleiner et al[17]	2010	4	Case- control study	16 MS/16 controls	Sniffin' Sticks TDI	MS: 50% hyposmia The EDSS score inversely correlated with the identification subtest
	Goektas et al[18]	2011	4	Cross-Sectional case control study	36 MS/36 controls	Sniffin' Sticks TDI	44.4% of MS patients with olfactory alteration OB volume correlated with olfactory function.

							Identification scores: correlated with neurological scores.
	Lutterotti et al[19]	2011	4	Case- control study	50 MS/30 controls	Sniffin' Sticks TDI	MS scored worse than controls on TDI, TH, ID Worsened smell threshold earlier in disease and then impaired identification with widespread chronic disease
	Dahlslett et al[20]	2012	4	Case- control study	30 MS/30 controls	Olfactory event related potentials (OERP), Sniffin' Sticks TDI	Patients with MS scored worse on TDI. OERP 23.8% hyposmia. TDI 40% hyposmia. TDI score inversely correlated with EDSS score; Identification: inversely correlated with disease duration and EDSS
	Erb et al[21]	2012	4	Case- control study	30 MS/30 controls	Sniffin' Sticks TDI	Threshold and Discriminations. Scores were similar between MS patients and controls, whereas

							total TDI and the Identification values were poorer in MS. No correlation between the Fractional Anisotropy (FA) reduction in lesions and the EDSS or the TDI score. Identification: Correlation with FA values of lesions in the olfactory brain
	Silva et al[22]	2012	4	Case- control study	153 MS/165 controls	B-SIT	MS patients scored worse on the B-SIT compared to controls. Age, disease duration, education, EDSS, depression and MMSE.
	Rolet et al[23]	2013	4	Case series	50 MS patients	Sniffin' Sticks TDI	Olfactory dysfunction was 40% threshold, 18% discrimination and 10% identification.

							Identification: correlation positivity with EDSS and negatively with medical record. TDI was inversely correlated with disease progression
	Caminiti et al[24]	2014	4	Case- control study	30 MS/30 controls	OERPs	7/ 30 patients did not show OERP. 16/23 patients had amplitude significantly lower than control group
	Erb-Eigner et al[25]	2014	4	Case- control study	30 MS/12 controls	Sniffin' Sticks TDI	MS patients scored worse thasn controls. TDI score increased with decreased FA, increased MD and increased RD. FA decreased in olfactory structures. TDI correlated with EDSS
	Holinski et al[26]	2014	4	Case series	20 patients with MS	Olfactometer	25% hyposmic. Negative correlation of OB volume and H2S latencies.

							Hyposmic patients had smaller OB volume and higher volume of lesions in OB.
	Caglayan et al[27]	2016	4	Case- control study	29 MS /30 controls	Sniffin' Sticks TDI	MS patients had worse thresholds compared to controls. T, I, TDI correlated with age. TDI correlated with MMSE and EDSS.
	Jordy et al[28]	2016	4	Case- control study	100 MS/100 controls	CCCRC	Olfactory alteration was seen in 32% of MS patients compared to 3% controls.
	Kandemir et al[29]	2016	4	Case- control study	20 MS/20 controls	B-SIT	No difference in total smell scores and disease duration or relapse
	Li et al[30]	2016	4	Case- control study	26 MS/26 controls	T & T olfactometer test kit	42.3% had olfactory impairment but there was no difference between MS and controls groups. T&T correlated with EDSS.

							Olfactory bulb was smaller in olfactory dysfunction.
	Good et al[31]	2017	4	Case- control study	73 MS/73controls	UPSIT ODT	MS patients scored worse than controls on the UPSIT. ODT correlation with lesion volume
	Uecker et al[32]	2017	4	Case series	20 MS patients	Sniffin' Sticks TDI	50% hyposmia. No significant change during the follow-up. Discrimination correlated negatively with number of relapses; VAS correlated with the TDI score of the longitudinally tested patients
	Atalar et al[33]	2018	4	Case- control study	31 MS/24 controls	CCCRC	Smell identification, smell threshold, and mean olfactory scores were all worse compared to controls.

							Disease duration and and number of MS attacks and CCCRC scores were inversely correlated. The MOCA test scores and CCCRC scores/subscores were positively correlated.
	Bsteh et al[34]	2018	4	Case- control study	Relapse group MS 28/Stable group MS as controls 27	Sniffin' Sticks T (Only Threshold)	Olfactory threshold was impaired in patients with acute MS relapse. Relapse group MS EDSS < controls
	Ciurleo et al[35]	2018	4	Case series	30 RRMS	. CCCRC	MS olfactory alterations were related to disability progression and disease activity.
	Li et al[36]	2018	4	Case- control study	37 neuromyelitis optica (NMO) and 37 MS	T&T olfactometer, gray matter (GM) voxel-based morphometry, MRI	Olfactory deficits 51.4% NMO and 40.5% MS. NMO with ODF had olfactory bulbs < than MS with ODF
	Bsteh et al[37]	2017	4	Case-control study	RRMS 128/PMS 9	Sniffin' Sticks test TDI.	D and I worsened over 3 years. T impairment is transient and

							predicts inflammatory disease activity, while I and D are associated with disability progression.
	Carotenuto et al[38]	2019	4	Cross-Sectional case control study	55 MS/20 controls	UPSIT	Worsened score compared to controls. Scores on the SDMT, CVLTII, BVMT and COWAT were related to the olfactory test score.
Granulomatosis with Polyangiitis (GPA)	Göktas et al[39]	2010	4	Case series	9 GPA patients	Sniffin' Sticks TDI	GPA patients had olfactory dysfunction
	Laudien et al[40]	2009	4	Case series	76 GPA patients	Sniffin' Sticks TDI	14 (18.4%) with olfactory dysfunction
	Fasunla et al[41]	2012	4	Case-control study	16 GPA/16 controls	Sniffin' Sticks TDI	GPA patients scored worse than controls
	Proft et al[42]	2014	4	Case-control study	44 GPA/44 controls	Sniffin' Sticks TDI	GPA patients scored worse in all domains compared to controls, with 75% hyposmia. Discriminationn: lower scores with azathioprin

	Zycinska et al[43]	2016	4	Case series	43 GPA patients	Sniffin' Sticks TDI	74% of GPA patients had olfactory dyfunction, scoring below normal on TDI and all domains
Systemic lupus erythematosus (SLE)	Cavaco et al[44]	2012	4	Case--control study	85 SLE/85 controls	B-SIT	SLE and NPSLE scored worse on the B-SIT compared to controls. NPSLE: more olfactory dysfunction than controls or non-NPSLE patients
	Chen et al[45]	2019	4	Case--control study	65 SLE/50 controls	CCCRC	Olfactory dysfunction was correlated with SLE disease activity and presence of anti-P.
	Bombini et al[10]	2018	4	Longitudinal case control study	143 SLE/57 SSc/166 HC	Sniffin' Sticks TDI, MOCA, BAI, BDI, MRI, (anti-P) antibodies	Olfactory dysfunction 54.5% SLE, 59.3% SSc and 14.45% controls. Olfactory dysfunction was associated with age, inflammation and smaller hippocampi and amygdalae

							volumes. In SLE OD was associated with anti-P, anxiety and depression symptoms.
	Shoenfeld et al[46]	2009	4	Case-control study	50 SLE/50 controls	Sniffin' Sticks TDI	Patients with SLE scored worse on TDI than controls
Rheumatoid arthritis (RA)	Steinbach et al[47]	2011	4	Cross sectional, case-control study	111 patients	Sniffin' Sticks TDI	Patients with RA scored worse on overall TDI and Threshold compared with controls. No correlation with disease activity, severity, extra-articular manifestations or autoantibodies
Myasthenia gravis (MG)	Leon-Sarmiento et al[48]	2012	4	Cross sectional, case-control study	27MG, 11 polymiositis/ 27 HC	UPSIT	MG UPSIT< control; polymiositis UPSIT < controls
	Tekeli et al[49]	2015	4	Case-control study	30 MG/30 controls	Sniffin' sticks test TDI	MG patients showed significantly lower olfactory and gustatory scores than controls Olfactory loss correlated with the severity of the disease

	Leon-Sarmiento et al[50]	2013	4	Literature review January 1950 through December 2012	Case reports	N/A	MG associated with olfactory impairment
Neuromyelitis optica (NO)	Zhang et al[51]	2015	4	Case-control study	49 NO/26 controls	T&T olfactometer	NMOSDs: 53% olfactory dysfunction patients had smaller OB volume than did patients without it or controls. Both detection and recognition thresholds for olfaction were negatively correlated with OB volume
Behçet's disease (BD)	Veyseller et al[52]	2014	4	Case--control study	30 BD/30 controls	CCCRC	BD patients scored worse than controls
	Akyol et al[53]	2016	4	Case-control study	50 BD/46 controls	Sniffin' Sticks TDI	BD patients scored worse on TDI and identification domain compared to controls
	Doğan et al[54]	2017	4	Case-control study	16 BD/16 controls	CCCRC	BD patients scored worse than controls. Parenchymal

							involvement led to worse scores
Mikulicz's disease (MD)	Takano et al [55]	2011	4	Case series	44 patients with MD	T &T olfactometer	45% patients had olfactory abnormalities Association of IgG4-positive plasmacytes in the nasal mucosa with olfactory abnormalities.

RRMS: relapsing-remitting multiple sclerosis; PMS: progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; DMT: disease-modifying therapy; BDI: Beck Depression Index; MMSE: mini-mental status examination; SDMT: Symbol Digit Modalities Test; University of Pennsylvania Smell Identification Test (UPSIT); Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT II); Brief Visuospatial Memory Test; (BVMT), Paced Auditory Serial Addition Test (PASAT); Controlled Oral Word Association Test (COWAT); Modified Fatigue Impact (MFI); Beck Depression Inventory (BDI); MSSS: Multiple Sclerosis Severity Score; AR – Actual Reality; BICAMS – The Brief International Cognitive Assessment for MS; BMS: burning mouth syndrome

- **Autoimmune diseases are a potential cause of olfactory dysfunction.**
  Aggregate grade of evidence: C (Level 2: 1 study, Level 4: 55 studies)

SECTION: IX. Pathophysiology

G. Related to underlying systemic disease

2) Vitamin-mineral deficiency

Vitamin and minerals play a crucial role in healthy maintenance of the olfactory mucosa, neuronal pathway and repair mechanisms, and disorders involving them can therefore derange the system.

Zinc is widely known to be a trace metal involved in the enzyme activity of cell proliferation.[1] As a result, it has been considered an important element when maintaining olfactory function. Deficiency in this trace metal has been linked with anosmia, but an excess

has also been associated with toxic effects upon the olfactory system.[1,2] Mechanisms for the later include inhibition of glutathione reductase, induction of necrosis, impairment of the electron transport chain and dysregulation of the copper or calcium homeostasis.[2,3,4] Furthermore, deficiencies in copper and nickel can produce similar smell alterations when assessing receptor response profiles.[1]

The olfactory receptor neurons primarily use glutamate, a neurotransmitter, during the excitation phase. Concentration variations can cause oxidative stress, as shown in Alzheimer's disease, and can occur secondarily to low vitamin E levels. These alterations in concentrations can ultimately lead to shifts in smell sensation.[5,6,7]

The mechanism for regeneration of the olfactory epithelium is not entirely clear, though specific pathways have been noted. Of these, vitamin A and its metabolites play an important role in tissue development and regeneration, with deficiencies implicated during olfactory embryogenesis and adult regeneration.[1,8,9]

B vitamins, including vitamin B6 and B12, play a crucial role in growth and development, specifically in nerve perseveration of the smell sensation. Vitamin B12 can affect nerve function in multiple locations, including the spinal cord, brain, optic nerve and peripheral nerves. With regards to olfaction, the mechanism of action is similar and can produce clinically symptomatic patients through deficiencies, though no difference in treatment.[1,10]

As shown through the importance of multiple vitamins and minerals, ultimately malnutrition can have a significant negative effect upon the olfactory organ. This can occur through protein and calorie deficits, total parenteral nutrition without adequate replacement, specific vitamin or mineral insufficiency or other dietary deficiencies. Although it would be mechanistically reasonable to consider vitamin and mineral deficiencies to cause olfactory dysfunction, there is no high level data currently to prove it.

SECTION: VII. Pathophysiology

G. Related to underlying systemic disease

3) Endocrine related

There are multiple endocrine disorders that can potentially affect olfactory mechanisms. Endocrine dysfunction can produce changes within the mucosal lining of the nose, the olfactory neural pathway or the olfactory repair mechanisms.

Disorders involving the hypothalamus can include hypothalamic dysfunction, which can lead to primary amenorrhoea and occasionally anosmia. In the same vein, patients with Froehlich syndrome, or adiposogenital dystrophy, suffer with smell deviations following damage to the arcuate nucleus and ventromedial nuclei of the hypothalamus.[1] Subsequent lack of hormone secretion from the anterior pituitary causes delay in normal puberty and its associated features.[1,2]

The pituitary gland itself, while crucial in various homeostatic functions, also plays an important role in olfaction. Endocrinologic manifestations of Cushing's syndrome can include inappropriate ADH secretion, catecholamine secretion, hyperprolactinemia and ACTH secretion. There is the potential for the subsequent symptoms associated with these derangements to include anosmia.[2] On the other hand, patients with adrenocortical insufficiency (at times secondary to a pituitary cause), also called Addison's disease, have a decreased ability to recognize odors. This is primarily related to the effects of hormonal reduction on smell function, but also due to the actions of those hormones on stem cells in the olfactory epithelium which induce maturation and differentiation.[3,4] Acromegaly and gigantism, secondary to hypersecretion of growth hormone and in turn IGF-1, are chronic, progressive, multisystem diseases. Part of the spectrum of clinical features can include hyposmia or anosmia. It is also worth noting that those with de Morsier's syndrome, septo-optic dysplasia, can have symptoms of anosmia secondary to pituitary variability.[1,5]

Patients with hypothyroidism have similar impairments in smell recognition secondary to deficient hormonal effects on the olfactory organ[6]

Other deviations resulting in olfactory variations can affect the olfactory bulb and receptor environment. Kallman's syndrome, otherwise known as hypogandotrophic hypogonadism, is an X-linked neuronal migrational disorder which causes anosmia secondary to aplasia of the olfactory bulb.[7,8] Turner's syndrome shares some parallel symptomology to Kallman's syndrome, including olfactory dysfunction, but with markedly different etiology.[9] As

noted in the section above, Sjogren's syndrome patients can suffer with excessive dryness of the nasal mucosa, as evidenced in atrophic rhinitis, with resultant olfactory dysfunction secondary to loss of moisture within the receptor environment. This ultimately leads to diminished chemoreception and transduction, and effects upon the HPA axis.[1,110] Interestingly, normal changes during pregnancy can result in notable alterations in perception of smells secondary to hormonal changes in the mucosa. These changes can be responsible or manifest as either hyperosmia, hyposmia or anosmia, with most cases temporary in duration until time of delivery.[11]

Finally, a combination of the secondary neurodegeneration and microvascular disease associated with diabetes mellitus (DM), results in a significant proportion of patients with DM suffering with diminished smell sensation.[12,13] Though this can be gradual in onset, and often undetected, there seems to be no correlation between diabetes duration and prevalence of olfactory dysfunction.

Table VII.10. Section Evidence Summary Table: Related to Endocrine Diseases

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical Endpoint	Conclusion
Gleeson et al[1]	2011	5	Evidence based review	Medline search using olfaction, smell, anosmia, dysosmia, phantosmia, odor identification, odor threshold, odor discrimination, olfactory epithelium, olfactory bulb and UPSIT.	Multiple psychometric measure of smell	Several endocrine disorders evidence disorders of smell
Sykiotis et al[2]	2010	4	Retrospective cohort study	90 men with Idiopathic hypogonadotropic hypogonadism	Subjective smelling ability	Patients with Idiopathic hypogonadotropic hypogonadism (IHH)

				undergoing long-term pulsatile GnRH treatment		with anosmia Kallmann syndrome (KS) can have variation in subjective smell ability based on whether the underlying genetic mutation is only affecting the hypothalamus vs. whether patients also have primary testicular and/or pituitary mutation.
Henkin et al[3]	1966	4	Prospective case-controlled study	41 normal volunteers, 56 patients with acute and chronic diseases, 2 patients with anterior pituitary insufficiency and 9 patients with adrenal cortical insufficiency	Threshold and recognition olfactory testing	Olfactory ability is markedly decreased in patients with untreated adrenal insufficiency
de Gennes et al[5]	1970	4	Case series	7 cases of patients with De Morsier's syndrome	Subjective smelling ability	All patients suffered with hypogonadotrophic hypogonadism with anosmia
McConnell et al[6]	1975	3	Prospective cohort study	15 patients with untreated primary hypothyroidism	Threshold and recognition olfactory testinh	Taste and smell defects are common clinical abnormalities in

				assessed pre and post treatment with thyroxine		primary hypothyroidism. These defects may contribute to the anorexia and lack of interest in eating which are frequently observed.
Stamou et al[7]	2018	5	Literature review of Kallman's syndrome	Patients with IGD	N/A	The clinical spectrum of IGD includes a variety of disorders including Kallmann Syndrome (KS), i.e. hypogonadotropic hypogonadism with anosmia, with high variability in the type and number of genetic mutations that can lead to this and other IGD related disease states.
Ros et al[9]	2012	3	Cohort controlled study	1) 30 Turner Syndrome patients 2) 14 age matched patients with other congenital hypogonadisms 3) 43 age matched healthy controls	BAST-24 olfactory testing	Patients with Turner Syndrome show impairment of smell but not of taste, compared to those with other congenital hypogonadisms as well as healthy

						controls taking contraception.
Kamel et al[10]	2009	3	Cohort-matched, prospective, cross-sectional study	1) 28 patients with Sjogren's Syndrome (SS) 2) 37 matched controls	Following administration of smell and taste testing, and completion of quality of life assessment.	Several endocrine abnormalities may play a role in the development of pSS, with abnormal HPA axis seen in a fifith and hypothyroidism seen in many patients. Impairment of chemosensory perception occurred in the SS group compared with age- and gender-matched controls.
Cameron[11]	2014	5	Literature review regarding effects of pregnancy on olfaction	Pregnant women with smell alteration	Measures of self-report, olfactory thresholds, odor identification, intensity and hedonic ratings, and disgust	The significant hormonal changes that take place during pregnancy can lead to hyperosmia, hyposmia, anosmia, and altered hedonistic response to odors. These changes are usually temporary and resolve after delivery.
Chan et al[12]	2017	4	Cross sectional study	3151 total NHANES participants with no diabetes, diabetes	Following collection of data regarding	Amongst diabetics, there was a significant trend to

				conservatively managed, diabetes controlled with oral medication, diabetes controlled with insulin	self-reported olfactory function	severe hyposmia/anosmia. No association was observed between diabetes duration and prevalence of olfactory dysfunction.
Brady et al [13]	2013	3	Cohort study	1. 19 healthy controls 2. 19 patients with non-complicated DM 3. 15 patients with DM and neuropathy without neuropathic pain 4. 21 patients with DM and neuropathy and neuropathic pain	Sniffin' Sticks	Patients with DM score worse on olfactory testing compared to controls, but only in groups with peripheral neuropathy. Severity of neuropathy or neuropathic pain did not correlate with severity of olfactory dysfunction.

- **Underlying endocrine disorders can affect the functionality of the olfactory system.**
  Aggregate Grade of Evidence: C (Level 3: 4 studies; Level 4: 4 studies; Level 5: 3 studies)

SECTION: VII. Pathophysiology

G. Related to underlying systemic disease

4) Renal failure

Our systematic literature review identified that patients with CKD and ESKD commonly experience olfactory impairment— a finding consistent with narrative reviews by Raff et al,[1] Landis et al,[2] and recently by Robles-Osorio et al[3] . Controversies persist, regarding which aspects

of olfaction are affected in renal patients, or whether undergoing dialysis alleviates olfactory impairment.

Kidney disease affects odor identification capacity,[1,2,4] and olfactory dysfunction correlates with the severity of kidney disease.[5,6] Odor discrimination is also diminished in renal patients.[4,7–9] Results concerning odor detection threshold in these patients are conflicting, describing either no change[4,10,11] or significant impairment.[6] Most early studies, however, suffered sample size limitations.[2,7–9]

Recently, Koseoglu et al[12] reported impaired odor identification, discrimination, and threshold in non-diabetic patients with renal failure versus control participants. This study found that ~80% of renal patients experience olfactory impairment and suggested that dialysis may improve olfaction.

In the largest study to date (n=161), Nigwekar et al[13] reported odor identification impairment in most patients with CKD (~70%) and ESKD (~90%). Detection threshold was comparable between CKD patients and control participants, but higher in ESKD patients.

Proposed explanations for olfactory impairment in renal patients[6] range from accumulation of uremic toxins impairing olfaction[14,15] or inducing polyneuropathy,[16] to nutrient removal by dialysis impairing regeneration and renewal of olfactory cells.[9] Despite uremia being a previously accepted widespread explanation,[15] Raff et al[1] found no correlation between accumulated uremic toxins and impaired olfaction in ESKD patients. Notably, this olfactory impairment appears to be physiologically reversible.[17] Improving olfaction in kidney transplant recipients also attests to the reversibility of ESKD-associated olfactory losses.[6]

Earlier studies reported that kidney patients are unaware of their disease-associated olfactory decline.[2,4,18] Self-assessments of smell and taste are similar in control, CKD, and ESKD patients, despite significant differences on formal testing in identification among them and in threshold between CKD and ESKD[13]—not surprisingly for mild hyposmia.[19,20] However, many patients do complain that the smell and taste of food are less pleasant than before renal impairment.[9,10,21,22]

Reports on the effect of dialysis on olfactory losses are inconsistent,[15] ranging from improvement after hemodialysis,[11] or no change,[6] to a slight worsening of olfaction.[7,8] Further assessments in larger numbers of patients are required.

SECTION: VII. Pathophysiology

H. Related to sinonasal or intracranial tumor

Sinonasal or intracranial neoplasms may lead to olfactory dysfunction via anatomic obstruction, direct tumor involvement or iatrogenically from tumor resection. Within this setting, smell loss can occur from either a conductive or neurosensory mechanism. Conductive olfactory loss results from anatomical obstruction of nasal airflow to the olfactory cleft and neuroepithelium.[1] Neurosensory deficits reflect damage or dysfunction to the olfactory neural pathway, typically from tumor involvement of the olfactory epithelium or bulb or higher processing centers such as the prefrontal or temporal lobe.[2-5]

Sinonasal tumors, such as squamous cell carcinoma, inverted papillomas, and esthesioneuroblastomas, often present with unilateral more than bilateral symptoms.[3,6-9] Esthesioneuroblastomas, which originate from the basal progenitor cells within the olfactory neuroepithelium, can present with nasal airway obstruction, epistaxis, and/or olfactory disturbances.[6,7] Similarly, intracranial neoplasms within the anterior cranial fossa, such as olfactory groove meningiomas, supratentorial meningiomas, frontal lobe gliomas, craniopharyngiomas, and pituitary neoplasms with suprasellar spread, can present with smell disturbances due to their compression or invasion of the olfactory nerves.[9-12]

Iatrogenic interventions within the nose for sinonasal or intracranial tumor extirpation can cause both transient and permanent olfactory loss.[13,14] The disturbance in olfactory function from surgery can occur through four means: mechanical injury, airflow modification, vascular/neural injury, and other.[1,8] Mechanical injuries reflect direct trauma to the olfactory neuroepithelium, such as traction or thermal injury to the olfactory filia or direct resection for tumor extirpation. Airflow modifiers represent any anatomical changes, like scarring, which prevent airflow to the olfactory cleft and mucosa. Additionally, transient hyposmia may occur

due to post-operative edema or packing. Vascular injury arises from iatrogenic ischemia to the olfactory epithelium while neural compromise may stem from a postoperative infection. Other mechanisms include medications and general anesthesia.[1,8,15]

While minimally invasive endoscopic skull base approaches have allowed reduction in morbidities associated with traditional open approaches, they require maximal exposure of the skull base, endangering significant portions of the peripheral olfactory structures.[1,16,17] Contemporary endoscopic approaches have been shown to preserve olfactory function when compared to traditional transseptal microscopic approaches.[18,19] However, expanded endonasal approaches may have a higher risk of olfactory injury when compared to limited transsphenoidal approaches.[1]

Olfactory preserving techniques have been described to curtail the risk of olfactory disturbance. These include preservation of the septal olfactory strip, avoidance of electrocautery during nasoseptal harvest, limiting the elevation of a pedicled nasoseptal mucosal flap, and preservation of the middle turbinates and upper 2/3 of the superior turbinates.[16,17,20-24] For select intracranial tumors that are unilateral and amenable to access via only one nostril, a unilateral endoscopic transnasal approach with preservation of the contralateral olfactory cleft and bulb has been proposed to assist with smell preservation.[25,26]

SECTION: VII. Pathophysiology

I. Related to increasing age

Olfactory dysfunction has a well-established association with advancing age. A systematic review and meta-analysis of 25 individual studies, including 175,073 healthy subjects with a mean age of 63.5 years (range 18-101) cites an overall population prevalence of 22.2%.[1] This rate rises to 34.5% in studies with a mean age over 55 compared with 7.5% in studies with a mean age below 55. Another meta-analysis using effect size identifies the most significant decrease in olfaction begins in the 5th decade of life.[2] Odds ratios for hyposmia range from 1.06 to 1.79 for every 5 year increment in age.[3–5] Individual cross-sectional studies have found rates of hyposmia in 13.9-50% of individuals over 65 and up to 80% in those over 80.[6–12] Longitudinal

studies have supported the findings of cross-sectional studies with one citing an overall 5-year incidence of developing olfactory dysfunction in 12.5% of previously normosmic older adults, ranging from 4.1% in those aged 53-59 and up to 47.1% in those aged 80-97.[4] Specific risk factors appear to be involved in decreased olfaction, including male sex, concurrent sinonasal disorders, smoking, alcohol abuse, obesity, low socioeconomic status, minority status, and caregiver dependency, while other factors appear protective, such as regular exercise.[4,13–16]

An initial improvement in olfactory ability through childhood is followed by deterioration in later adulthood, possibly because odor identification requires both detection and cognitive processing with associated discrimination, recognition, and name retrieval. Odor identification in children under 10 is worse than teenagers and adults, likely related to either underdeveloped cognitive processing or difficulty with testing methodology in this age group, and improves through the 2nd decade of life.[17,18] While some studies have suggested that odor detection thresholds (ODTs) and overall olfactory ability remain relatively stable from childhood through late adulthood, partly as a result of increased odor familiarity over time, most research has identified age as the most consistently proven risk factor for smell loss, with optimal olfactory performance in the 3rd to 4th decade of life followed by slow steady deterioration that accelerates after age 60 and becomes particularly severe after age 70 to 80.[1,5,6,10,17–26] Notably, 5-year mortality rates in these hyposmic elderly individuals has been found to be as much as 36% higher compared with normosmic counterparts, highlighting the clinical significance.[8,12,27]

Several underlying pathophysiologic mechanisms have been proposed to explain the association between age and olfaction. Odor identification requires both peripheral sensory perception as well as central cognitive processing, and insults at any point along the pathway may compromise olfaction. Possible mechanisms associated with the olfactory neuroepithelium include age-related atrophy, cumulative exposure to pollution, toxins, and bacteria, decrease in mucosal blood flow, chronic inflammation, impaired mucociliary function, decreased regenerative capacity, replacement with respiratory epithelium, decrease in the number and specificity of olfactory receptors, reduction in the size and number of patent foramina in the cribriform plate, impairment of immunologic and enzymatic defense mechanisms, and cellular accumulation of amyloid and tau filaments.[8,13,28–30] The olfactory bulb may demonstrate

atrophy, loss of neuronal elements, and decreased laminae and glomeruli with age, as well as accumulation of tau and α-synuclein.[8,13,31,32] At higher level processing centers, olfactory loss may be associated with age-related cortical degeneration, specifically reduction in the volume or function of the hippocampus, amygdala, piriform cortex, orbitofrontal cortex, anterior olfactory sulcus, and cholinergic system.[8,13,15,33] Some studies suggest a decline in the trigeminal contribution to olfaction may play a role, although this is unconfirmed.[15] Genetic predispositions exist for age-related hyposmia, including the val66met polymorphism of BDNF and the ε4-allele of human apolipoprotein E gene.[8] Despite the contribution of genetics, which has been shown to influence the intensity and perception of olfaction, twin studies suggest environmental factors likely contribute to a greater degree than genetic factors with increased age.[30,34]

While broad age-related trends are well-established, significant heterogeneity exists between study findings due to variation in study populations, olfactory instruments, and classification of dysfunction. Studies sometimes designate dysfunction based on normative age-specific cutoffs rather than ideal levels, limiting comparison.[23] Subjective self-assessment yields a much lower prevalence than objective testing, indicating a significant lack of sensitivity in relying on patient report alone, with up to 75% of patients not recognizing their own smell loss.[1,6,8,12,15,22,35,36] Sensitivity can be improved by querying specifically about age-related changes in smell function.[37]

Given the risks associated with smell loss and the wide prevalence despite lack of recognition, consideration may be given for brief testing to screen for severe dysfunction in aging individuals. Consensus in standardized objective olfactory instruments and definitions of dysfunction should be sought to more effectively compare outcomes and share knowledge for this common and important problem.

Table VII.11. Section Evidence Summary Table: Related to Aging

Study	Year	LOE (1 to	Study Design	Study Groups	Clinical Endpoint	Conclusion

		5)				
Desiato et al[1]	2020	1	Meta-analysis and systematic review (25 studies)	Healthy populations (varied recruitment methods)	Subjective and/or objective evaluation of OD	OD is greater with age, use of objective testing instead of subjective testing is more accurate, and expanded over brief identification tests give better information
Zhang et al[2]	2017	1	Meta-analysis (13 studies)	Healthy adults A) Age 30-39.9 vs 40-49.9 B) Age 35-55 vs >55	Objective (UPSIT, Sniffin' Sticks, BAST-24, BSIT)	OD on average starts in the 5th decade of life
Adams et al[35]	2017	2	Cross-sectional study	NSHAP respondents	Subjective and objective (OFFE)	Decreased subjective recognition of OD with age
Brämereson et al[6]	2004	2	Cross-sectional study	Adult inhabitants of Skövde, Sweden	Objective (SOIT)	OD overall prevalence 19.1%, increases with age
Hoffman et al[12]	2016	2	Cross-sectional study	NHANES respondents	Subjective and objective (PST)	OD overall prevalence 12.4%, 39.4% in 80+, poor sensitivity of self-report
Hummel et al[21]	2007	2	Cross-sectional study	Healthy children in Dresden, Germany	Objective (Sniffin' Sticks, ERPs)	Children progressively attach more meaning to odors with age, improving identification
Kern et al[26]	2014	2	Cross-sectional study	NSHAP respondents	Subjective and objective (OFFE)	OD increases with age and male sex
Larsson et al[25]	2000	2	Cross-sectional study	Adult Swedish Twin Registry respondents	Objective (Nat'l Geographic Smell Survey)	Odor detection and identification impaired with age

Liu et al[3]	2016	2	Cross-sectional study	NHANES respondents	Objective (PST)	OD overall prevalence 13.5%, increase with age, higher in men
Masala et al[24]	2018	2	Cross-sectional study	Adult participants in Sardinia, Italy	Objective (Sniffin' Sticks)	Smell loss notable over age 55
Mullol et al[22]	2012	2	Cross-sectional study	Newspaper readers in Catalonia, Spain	Subjective and objective (proprietary 4 scent test)	Odor detection declines with age, but recognition and identification increase up to 4th decade, declines after 6th
Noel et al[5]	2017	2	Cross-sectional study	NHANES respondents	Subjective and objective (PST)	Increased OD with age, male sex, minority status
Oleszkiewicz et al[18]	2019	2	Cross-sectional study	Healthy adults and children (multicenter)	Objective (Sniffin' Sticks)	Best performance at 20-30, worst performance <10 and >70
Pinto et al[16]	2014	2	Cross-sectional study	NSHAP respondents	Objective (OFFE)	African Americans have worse OD compared to other races in peer age groups after correcting for confounders
Rawal et al[37]	2016	2	Cross-sectional study	NHANES respondents	Subjective	OD prevalence increases with age (32% above 80)
Rawson et al[29]	2012	2	Cross-sectional study	Healthy volunteers in Philadelphia, PA, USA	Objective (scent thresholds for 2 odors, olfactory biopsies with fluorescence imaging)	Loss of olfactory sensory neuron specificity with age
Sama-ul-Haq et al[31]	2008	2	Cross-sectional study	Cadaver study	Mitral cell number and diameter	Number and diameter of mitral cells decreases with age
Schubert et al[7]	2012	2	Cross-sectional study	Beaver Dam Offspring	Subjective and objective	OD 0.6% <35 yo compared with 13.9% >65 yo

				Study participants	(SDOIT)	
Schubert et al[20]	2017	2	Cross-sectional study	EHLS adult participants	Objective (OLFACT-RL)	ODT worse in older adults
Segura et al[33]	2013	2	Cross-sectional study	Healthy older adults in Barcelona, Spain	Objective (UPSIT, MRI of olfactory centers)	Age-related OD accompanied by characteristic degenerative cortical changes
Sorokowska et al[17]	2015	2	Cross-sectional study	Healthy volunteers (multicenter)	Subjective and objective (Sniffin' Sticks)	Higher OD <20 yo and >60 yo
Wilson et al[27]	2011	2	Longitudinal population-based study	Elderly volunteers in Chicago, IL	Objective (BSIT), mortality	OD associated with increased mortality
Xu et al[19]	2020	2	Cross-sectional study	NSHAP respondents	Objective (Sniffin' Sticks)	Odor sensitivity and identification both decrease with age, identification more affected by cognition
Yousem et al[32]	1998	2	Cross-sectional study	Healthy volunteers in Philadelphia, PA, USA	Objective (UPSIT, MRI of olfactory centers)	Olfactory bulb and tract volume increase up to 4th decade then decrease, but not correlated with UPSIT
Doty et al[10]	1984	2	Cross-sectional study	Healthy volunteers in Philadelphia, PA, USA	Objective (UPSIT)	Best olfactory performance between 20 and 40, high rates of anosmia in the elderly
Hoffman et al[12]	2006	2	Cross-sectional study	NHIS respondents	Subjective	Increased risk for OD over age 55
Murphy et al[11]	2002	2	Cross-sectional study	EHLS adult participants	Subjective and objective (SDOIT)	Overall OD prevalence 24.5%, in >80 yo 62.5%, accuracy of self-report worsens with age

Schubert et al[4]	2011	2	Longitudinal population-based study	EHLS adult participants	Objective (SDOIT)	Incidence of OD increases with OR of 1.78 for every 5-year increment of age
Sulmont-Rossé et al[14]	2015	2	Cross-sectional study	Aupalesens project participants	Objective (ETOC, proprietary discrimination tests)	Link between caregiver dependence and OD independent of age

OD = olfactory dysfunction
NSHAP = National Social Life, Health, and Aging Project
NHIS = National Health Interview Survey
NHANES = U.S. National Health and Nutrition Examination Survey
EHLS = Epidemiology of Hearing Loss Study
SOIT = Scandinavian Odor Identification Test
UPSIT = University of Pennsylvania Identification Test
BSIT = Brief Smell Identification Test
SDOIT = San Diego Odor Identification Test
BAST-24 = Barcelona Smell Test-24
OFFE = Olfactory Function Field Exam
PST = Pocket Smell Test
OLFACT-RL = Osmic Enterprises Olfactometer
ERP = Event-related potential

- **Increasing age after the fourth decade is associated with decreasing olfactory function.**

  Aggregate Grade of Evidence: B (Level 1: 2 studies, Level 2: 27 studies)

SECTION: IX. Pathophysiology

J. Related to neurodegenerative disease

Over the last decade, multiple studies have demonstrated that olfactory dysfunction may be the earliest sign of neurodegeneration, affecting those with subjective cognitive decline (SCD), mild cognitive impairment (MCI), Alzheimer's disease (AD) and Parkinson's disease (PD).
In preclinical AD, patients can experience SCD which causes them concern although classic neuropsychological tests are not able to detect any change in cognition at that time.[1] A meta-analysis of five studies evaluating olfactory function in individuals with SCD and in healthy older adults found that there was a significant difference, with slight relative impairment in those with SCD.[2]

In the Mayo Clinic Study of Aging, participants were classified as having normal cognition, amnestic MCI (aMCI), nonamnestic MCI (nMCI) or dementia. This population based prospective cohort study found that olfactory impairment is associated with aMCI and with the progression of aMCI to AD dementia.[3]

A quantitative meta-analysis was performed on 31 previous studies including the one above comparing olfactory function in patients with MCI and healthy older adults. This also found that olfactory deficits are present and robust in patients with MCI compared to healthy older adults, and that the most prominent alteration appears to be in olfactory identification scores.[4]

The association between smell loss and PD has long been known, but the ability to predict the development of PD using olfactory function as a predictor has only been studied more recently. A systematic review (SR) and meta-analysis was published in 2019 evaluating the use of hyposmia as a predictive factor for PD. Of 1774 studies retrieved in their search, only seven met requirements for inclusion. Inclusion requirements were a prospective human study, baseline olfactory test prior to any diagnosis of PD, reported relative risks 9RR) odds ratios (OR) and hazard ratios (HR) with a 95% confidence interval (CI) or report data with which those could be calculated. Based on the data from these studies, the authors found that hyposmia leads to a 3.84 fold increase in risk of developing PD compared to normosmic patients.[5]

Interestingly, a recent meta-analysis also attempted to compare the olfactory functional deficits between AD and PD patients to determine which olfactory measures may be most useful in screening for these distinct patient populations. They found that all olfactory

measures were affected in patients with AD and PD in comparison with healthy controls, but that identification (and in AD, recognition) were more strongly affected than detection. After multiple post-hoc tests were performed, olfactory detection appeared to be more strongly affected in PD compared to AD.[6]

Although AD and PD are two of the most common and widely known types of dementia, there are several others. Olfactory dysfunction is seen in frontotemporal dementia, with difficulty in detection and recognition but preserved identification in the behavioral variant and dysfunction seen in the semantic variant but with not enough data to further parse any difference in testing modalities.[7] Lewy body dementia (LBD) and Rapid eye-movement sleep behavior disorder (RBD), now suspected as a potential prodrome to LBD and PD, have also both been associated with olfactory deficits, but only in smaller and lower LOE studies thus far.[8,9] As more subtypes of dementia emerge, it is likely that olfactory function may predict these as well, as the olfactory system appears to be the "canary in the coal mine" of neurocognitive ability.

Table VII.12 Section Evidence Summary Table: Related to Neurodegenerative Disease

Author	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Jobin et al[2]	2021	3a	Meta-analysis of case-control studies	1) 264 patients with SCD 2) 334 healthy controls	Olfactory psychophysical examinations of identification, detection, threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Quantitative meta-analysis indicates slight olfactory deficits in individuals with SCD compared with healthy controls
Roberts et al[3]	2016	1b	Prospective cohort study	1) Patients with dementia 2) Patients with aMCI	Olfactory psychophysical examination	Quantitative analysis indicating significant olfactory impairment in aMCI

				3) Patients with nMCI 4) healthy controls	of identification (B-SIT)	compared with controls, which was also associated with progression to AD dementia.
Roalf et al[4]	2017	3a	Meta-analysis of case-control and cohort studies	1) 1993 patients with MCI 2) 2861 healthy controls	Olfactory psychophysical examinations of identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Quantiative meta-analysis indicates robust olfactory deficits in patients with MCI. Olfactory identification test may be useful in early screening for cognitive impairment and dementia.
Sui et al[5]	2019	2a	Systematic Review and meta-analysis	1) 3272 patients with hyposmia 2) 5288 normosmic controls	Olfactory psychophysical examinations of identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks) and cognitive testing for PD diagnosis	Quantitave meta-analysis indicating a 3.84 fold increase in risk for developing PD in patients with hyposmia compared to normosmic controls.
Rahayel et al[6]	2012	2a	Systematic Review and meta-analysis	1) 39 studies on AD 2. 42 studies on PD	Olfactory psychophysical examinations of	Quantitative meta-analysis indicates significant olfactory dysfunction is

					identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	evident in both AD and PD, with AD patients showing a more significant deficit in identification and recognition while PD patients had those but also had significant difficulty with detection.
Silva et al[7]	2019	2a	Systematic review and meta-analysis	1. 189 patients with FTD 2. 225 healthy controls	Olfactory psychophysical examinations of identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Quantitative meta-analysis indicates olfactory dysfunction is evident in patient with FTD, with detection and discrimination affected and identification relatively spared in the behavioral variant, and dysfunction present in the semantic variant with more data needed to differentiate between testing modalities in that group.

Driver-Dunckley et al[8]	2014	2b	Prospective cohort study	1. 10 patients with PD 2. 13 patients with LBD 3. 69 controls	Olfactory psychophysical examinations of identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Post-mortem autopsy compared to prior baseline UPSIT testing demonstrated that both PD and LBD groups had lower UPSIT scores than healthy controls, with PD having the lowest scores.
Mahlknecht et al[9]	2015	2b	Prospective case series	34 patients with RBD	Olfactory psychophysical examinations of identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	The entire Sniffin' Sticks score as well as the identification subdomain had a diagnostic accuracy of predicting conversion to LBD of 82.4%. Relative risk for LBD in the lowest tertile of olfactory function was 7.3 compared to the top two.

Cognitive testing in Older Patients with Olfactory Deficits

Aggregate Grade of Evidence: A (Level 1: 1 study, Level 2: 5 studies, Level 3: 2 studies).

Benefit: Establishing baseline cognition and following this over time in older patients with olfactory deficit greater than that expected for age and no other clear etiology, allows for earlier recognition of MCI, AD, PD, and other forms of dementia.

Harm: Relatively low with potential to incite concern or anxiety about the potential of developing dementia in otherwise healthy individuals

Cost:

Direct: Low to moderate monetary cost involving additional testing

Indirect: Minimal

Benefits-Harm Assessment: Preponderance of benefit over harm.

Value Judgments: Olfactory deficits as well as overall cognition should be compared to peer age groups, as some diminution of ability in both respects is expected with the normal aging process.
Policy Level: Strong recommendation for baseline cognitive testing in older adults with olfactory deficit greater than that expected for age and no other clear etiology for smell dysfunction.
Intervention: Baseline cognitive testing by either primary care provider or neurologist in older adults with olfactory deficit greater than that expected for age and no other clear etiology for smell dysfunction.

SECTION: IX. Pathophysiology

K. Related to other neurotransmitter disease states (depression, schizophrenia, autism, etc.)

The olfactory sensory neural pathway includes numerous brain regions implicated in the pathophysiology of a number of developmentally-mediated neuropsychiatric disorders.[1–26] Notably, in the last two decades, the literature concerning psychophysical olfactory function and its associated structural brain, physiological and clinical correlates has exponentially grown, providing crucial insights into the developmental and clinical aspects of these neuropsychiatric disorders. Below is a review of four developmentally-linked psychiatric disorders including: 1) schizophrenia (SCZ), 2) autism spectrum disorder (ASD), 3) obsessive-compulsive disorder (OCD), 4) attention deficit/hyperactivity disorder (ADHD) and findings concerning psychophysical olfactory functioning in each.

Schizophrenia

Previous research has provided compelling support for the presence of olfactory dysfunction in patients with SCZ, with diffuse impairments across a wide variety of olfactory tasks being evident.[27–29] Results revealed moderate to large olfactory deficits in SCZ though significant heterogeneity was observed**.** Deficits across the psychophysical domains of odor: 1) identification (large effect size), 2) detection threshold (small-moderate effect size), 3) discrimination (moderate effect size), 4) hedonics (moderate effect size) and, 5) memory (large effect size) were seen. Across these five olfactory domains, among individuals with SCZ: 1) older

age, 2) being male, 3) greater duration of illness and, 4) medication with typical antipsychotics appeared to be associated with greater olfactory deficit.

Autism Spectrum Disorder

Atypical sensory processing issues have been specifically highlighted in the DSM-5 diagnostic ASD criteria and have been found to contribute to interpersonal, cognitive and behavioral problems in this disorder. Despite the latter findings, little attention has been given to chemosensory function in ASD. Review of the literature[26,30] concerning olfactory processing in ASD reveals a generally small to moderate, but homogeneous, pattern of deficits across the domains of odor: 1) identification (moderate effect size), 2) detection threshold (small effect size), 3) discrimination (small to moderate effect size), 4) intensity (small effect size) and 5) hedonics (small effect size). Across these five olfactory domains, among individuals with ASD: 1) younger age, 2) being male, and, 3) having lower Full-Scale IQ appears to be associated with greater olfactory deficit.

Obsessive-Compulsive Disorder

Numerous studies have linked emotions such as disgust with basic olfactory function, and the underlying neuroanatomy of the olfactory system suggests a link to the presumed orbitofrontal pathophysiology of OCD. Review of the literature[30] concerning olfactory processing in OCD revealed a generally moderate to large, but homogeneous, pattern of deficits across the domains of odor: 1) identification (moderate to large effect size), 2) detection threshold (small to moderate effect size), 3) discrimination (large effect size), 4) intensity (moderate to large effect size) and 5) hedonics (moderate-large effect size). While the literature on chemosensory dysfunction in OCD is still in its infancy, this review generally supports that patients with OCD who were: 1) younger, 2) male, 3) had more severe OCD symptoms and 4) taking psychotropic medications demonstrated greater olfactory impairment.

Attention Deficit/Hyperactivity Disorder

In ADHD, disruption of olfactory processing is thought to be related to dopamine metabolism and orbitofrontal cortex functioning, both known to be involved in the neurobiology of this disorder. Review of the literature[30] concerning olfactory processing in ADHD reveals a generally small magnitude and homogeneous pattern of deficits across the domains of odor: 1) identification (moderate effect size), 2) detection threshold (negligible effect size), 3) discrimination (negligible effect size), 4) intensity (small effect size) and 5) hedonics (negligible effect size). Overall, the literature concerning olfactory function in ADHD suggests that: 1) being male, 2) having lower intellectual skills, and, 3) the use of psychotropic medication was related to greater olfactory impairment.

Table VII.13. Section Evidence Summary Table: Related to Neurotransmitter Disease States

Author	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Moberg et al[27]	1999	1	Systematic Review	1) 787 Patients with DSM diagnosis schizophrenia 2) 662 healthy controls	Olfactory psychophysical examinations of identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Quantitative meta-analysis indicates substantial olfactory deficits, across all domains, are observed in patients with schizophrenia. The influences of gender, medication status, and smoking on effect sizes were not significant across studies
Nguyen et al[28]	2010	2	Systematic Review	1) Patients with DSM diagnosis of schizophrenia 2) healthy controls	Olfactory psychophysical examinations of	Qualitative review indicating significant olfactory impairment in schizophrenia with

					identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks); neuroimaging	discussion of neuroanatomical substrates.
Moberg et al[29]	2014	1	Systematic Review	1) 4,491 Patients with DSM diagnosis of schizophrenia 2) 875 Genetic and clinical patients at-risk for schizophrenia 3) 4,408 healthy controls	Olfactory psychophysical examinations of identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Quantiative meta-analysis indicates robust olfactory deficits in schizophrenia and at-risk youths. Olfactory measures may be a useful marker of schizophrenia risk status
Tonacci et al[26]	2017	2	Systematic Review	1) patients with ASD 2) healthy controls	Olfactory psychophysical examinations of identification, detection threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Qualitative review indicating possible olfactory impairment in ASD and other developmental disorders.
Crow et al[30]	2020	1	Systematic Review	1) 320 patients with ASD 2) 208 patients with OCD 3) 320 patients ADHD 4) 910 Healthy	Olfactory psychophysical examinations of identification, detection threshold, discrimination	Quantiative meta-analysis indicates olfactory dysfunction is evident in individuals with ASD and OCD, with small-to-negligible effects in ADHD.

					(e.g. UPSIT, Sniffin Sticks)	

Olfactory dysfunction is prominent in many neurodevelopmental disorders with neurotransmitter disruption.
In summary, the following statements can be made about olfactory dysfuction:
1. Robust, homogenous deficits in olfactory function are common in schizophrenia and these deficits do not correlate with gender, medication status, or smoking.
Aggregate Grade of Evidence: B (Level 1: 3 large quantitative meta-analytic studies that are consistent; 1 qualtiative review).
2. Olfactory dysfunction is prevalent and may be a core deficit in ASD and OCD, but not ADHD.
Aggregate Grade of Evidence: C (Level 4: 1 moderately sized quantitative meta-analytic study and 1 qualitative review).

SECTION: IX. Pathophysiology

L. Related to seizures, migraine, or other headache activity

Migraine and epilepsy are the two best known paroxysmal neurologic disorders. Olfactory disturbances are common in each disorder and may include olfactory hallucinations, changes in olfactory function or sensitivity, and intolerance to odors, particularly during acute attacks. Olfactory hallucinations have long been a known potential component of seizure activity or the aura that precedes it, but less well known is the potential for interictal olfactory deficit or dysfunction in patients with epilepsy. A 2019 systematic review and meta-analysis demonstrated that olfactory deficits were common in patients with epilepsy, being most prominent in patients with temporal lobe epilepsy (TLE) and mixed-frontal (M-F) epilepsy. Amongst patients with epilepsy, sex, age, smoking status, education, handedness, and age of illness onset were significantly related to olfactory performance.[1]

In a systematic review performed a year later, on patients with TLE, Hwang et al[2] found that olfactory testing could be used to differentiate TLE from other forms of epilepsy with high sensitivity and specificity, as well as being useful in predicting appropriate patient selection and outcomes from surgical intervention to treat these patients.

Olfactory hallucinations may accompany other sensations such nausea/stomach pain and fear in patients with epilepsy[3]. Less than 20% of patients with temporal lobe epilepsy experience olfactory hallucinations, and it is not necessarily more common than motor or sensory auras [4]. Mesial temporal lobe epilepsy typically results from functional or structural changes to areas of the limbic system, such as the amygdala and hippocampus. These structures of the olfactory cortex receive olfactory information from the olfactory bulb and have been shown to activate on functional MRI in response to odor intensity[5]. In a study of 12 temporal lobe epilepsy patients with olfactory auras (2 of which exclusively had structural lesions in the amygdala on neuroimaging), all patients had resolution of olfactory symptoms after mesial temporal lobectomy[3]. The prevailing view is that these changes explain change in smell and olfactory hallucinations [4] but another possibility is that changes in the olfactory bulb play a role [6].

Subjects with temporal lobe epilepsy and a unilateral epileptic focus perform worse on standard measures of olfaction. The impairment is typically bilateral and surgical treatment such as mesial temporal lobectomy may exacerbate the problem[7,8].

Due to the highly overlapping anatomy between the regions involved in smell and the regions involved in seizure activity, discussing olfaction and performing olfactory testing may be important in this patient population.

Table VII.14. Section Evidence Summary Table: Related to Seizures or Epilepsy						
Author	**Year**	**LOE**	**Study Design**	**Study Groups**	**Clinical Endpoint**	**Conclusion**
Kurshid et al[1]	2019	2a	Systematic review and meta-analysis	1) 912 patients with epilepsy 2) 794 healthy controls	Olfactory psychophysical examinations of identification, detection, threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Quantitative meta-analysis indicates significant olfactory deficits in patients with epilepsy, most prominent in TLE and M-F epilepsy.
Hwang et al[2]	2020	3a	Systematic review without meta-analysis	1) Patients with TLE 2) Patients with other forms of epilepsy	Olfactory psychophysical examinations of identification, detection, threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Systematic review confirmed significant olfactory deficit in patients with TLE, also noting the use of olfactory testing to differentiate TLE from other forms of epilepsy as well as using olfactory testing to predict patient selection and outcome in surgical procedures to treat it.
Chen et al[3]	2003	4	Case series	217 Chinese patients who underwent temporal lobectomy for	1) resolution of olfactory symptoms 2) Resolution of seizures	Resolution of olfactory auras after mesial temporal lobectomy in all patients

				medically intractable TLE	3) Clinical characteristics of patients with olfactory aura	

Olfaction can also be linked to headache syndromes on several levels: potent smells provoking headache, fear or sensitivity to smells being a component of headache, and smell being altered in patients with headache syndromes.

Emerging understanding of pathophysiology suggests multiple reasons for the olfactory changes which have been described in migraine. Functional changes in the limbic system[8], cortical spreading depression in the piriform cortex[9,10], activation of the amygdala [11] and the release of calcitonin gene-related peptide by olfactory stimuli [12] are among the factors which may explain this relationship. In one MRI study, patients with migraine and osmophobia had lower olfactory bulb volume than controls[13]. While most patients with migraine have normal olfaction [14,15], it may be impaired in a minority of more affected patients[16,17].

Osmophobia is the fear, dislike, or aversion to odors. Prior literature has cited osmophobia as being present in migrainous headaches with up to 95% prevalence, and yet it is not mentioned in the International Classification of Headache Disorders (ICHD).[18] Photosensitivity/photophobia and phonosensitivity/phonophobia are mentioned and noted as part of the diagnostic criteria, yet osmophobia is not. Whether it is truly present in such a large proportion of migraine is debated, but osmophobia is certainly one of the most common associated symptoms of migraine in patients of all ages[19,20] with a prevalence of 25-86% found in various clinical studies[21,22] A prospective study was performed on migrainous patients with (MA) and without

(MO) aura, as well as on episodic tension type headache (ETTH) patients. 67.2% of migraineurs reported osmophobia in at least a quarter of their attacks, whereas zero ETTH patients reported this as a symptom. The authors suggested this symptom as being useful to differentiate migraine without aura and ETTH, which is sometimes otherwise a difficult distinction.[23] This hypersensitivity to odors and even tastes may persist between attacks[24,25]. Olfactory stimuli such as smoke or perfume can precipitate migraine attacks [26] and pleasant odors such as lavender may improve it[28,29]. Osmophobia is most common in migraine, but has also been reported in other headache disorders such as cluster headache[30].

There are some data to suggest that while certain smells are particularly offensive to migraineurs, even when in between attacks, this does not change their baseline olfactory ability.[16] However, there are also data demonstrating that baseline olfactory acuity is more abnormal in migraine patients than in controls,[31] as well as evidence suggesting that olfactory bulb volume (OBV) is diminished in patients with migraine when compared to healthy controls, with no difference in olfactory sulcus length (OSL).[32]

Less than 1% of migraine patients report olfactory hallucinations, which usually correlates with osmophobia and migraine severity[33]. Phantosmia in migraine is almost always unpleasant and patients may be able to identify the specific odor. The duration of hallucinations in migraine exceeds epileptic phantosmia usually lasting 5-60 minutes, leading some to speculate it is a migraine aura [34]. More data are needed to determine the true extent of olfactory dysfunction in patients with primary headache syndromes.

Table VII.15 Section Evidence Summary Table: Related to primary headache syndrome						
	Year	**LOE**	**Study Design**	**Study Groups**	**Clinical Endpoint**	**Conclusion**
Terrin et al[23]	2020	1b	Systematic review and meta-analysis	1) 128 patients with MA 2) 5 patients with MO 3) 31 patients with ETTH 4) 21 patients with MO and ETTH 5) 7 patients with MA and ETTH 6. One patient with MA and ETTH	Presence of osmophobia before or during headache	Osmophobia is a specific clinical marker of migraine and can be used to distinguish migraine from other types of headache such as ETTH.
Saisu et al[16]	2011	3b	Prospective case-control study	1) Patients with MO 2) Patients with MA 3) Healthy controls	Olfactory psychophysical examinations of identification, detection, threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Comparison between groups demonstrated osmophobia in 63% of MO and MA groups, with MA having a worsened aversion than MO to all scents. 91% of migraine patients had normal smelling ability.
Whiting et al[31]	2015	3b	Prospective case-control study	1) 50 patients with migraine 2) 50 healthy controls	Olfactory psychophysical examinations of identification, detection, threshold, discrimination (e.g. UPSIT, Sniffin Sticks)	Migraine patients do not have a significant difference in olfactory ability during their attacks versus in between attacks, but they were more likely to have abnormal olfactory acuity compared to controls.
Aktürk et al[32]	2019	3b	Prospective case-	1) Patients with MO 2) Patients with MA 3. Healthy controls	OBV and OSL on MRI	Comparison between groups demonstrated significantly decreased

			control study			OBV in patients with migraine (both MA and MO) compared to healthy controls. There was no difference seen in OSL.
Stankewitz et al.[9]	2011	4	Case control	20 migraine patients with sex- and age-matched healthy controls	Amygdala activation on fMRI	Amygdala activation during migraine in response to olfactory stimulation
Demarquay et al.[10]	2008	4	Case control	11 migraineurs with OHS and 12 controls participated in a H(2)(15)O-positron emission tomography study.	Regional cerebral blood flow (rCBF)	Higher rCBF in the left piriform cortex and antero-superior temporal gyrus in migraineurs compared with controls during both olfactory and nonolfactory conditions

Olfactory Dysfunction related to Epilepsy

Aggregate Grade of Evidence: B (Level 1: 2 studies)

Olfactory Dysfunction related to Primary Headache Syndromes

Aggregate Grade of Evidence: B (Level 1: 1 study, Level 4: 3 studies).

SECTION: IX. Pathophysiology

M. Congenital

Unliked acquired smell loss, congenital smell loss is present at birth and may be either isolated or syndromic.[1] Isolated congenital anosmia (ICA) is a rare etiology (0-4% of smell loss) and is a diagnosis of exclusion in non-syndromic patients with no memory of smell, a history which may be difficult to accurately obtain.[1–4] Patients may seek care in childhood due to parental

concerns but often do not present until adulthood.[5] While patients may occasionally have specific anosmia for particular odorants, one study showed a 93.1% rate of total anosmia in patients with ICA.[6,7]

ICA may be due to sinonasal malformations impairing odorant transport to the olfactory neuroepithelium (e.g. choanal atresia, olfactory cleft maldevelopment), disrupted signal transduction, or pathology of cortical structures necessary for olfactory processing.[1] Characteristic MRI findings include underdevelopment of the olfactory bulb or sulcus, an imperforate cribriform plate, and/or distinct changes in the volume of cortical regions associated with olfactory memory.[8–12] Biopsies may yield respiratory rather than olfactory epithelium.[13] Genetic factors likely play some role and family clusters have been identified with CNGA2 and TENMI1 mutations on whole exome sequencing.[14–17]

Progress has been made to identify genes associated with syndromic presentations. Kallmann syndrome is a form of hypogonadotropic hypogonadism with up to 60% of patients experiencing anosmia.[18] Associations have been noted between anosmia and CHARGE syndrome, with CHD7 and other gene mutations identified on gene sequencing.[16,19] Congenital insensitivity to pain is associated with hyposmia through a SCN9A mutation.[20] Syndromic ciliopathies, such as Bardet-Biedl, have also been associated with congenital hyposmia from basic research on mechanisms[21,22] and by a match-controlled study.[23] Holoprosencephaly associated with absence of the entire olfactory apparatus leads to smell loss but often goes unnoticed.[1]

Population data rely on retrospective case series, case-control studies, and rare cross-sectional studies. Clinical experience at one high-volume center estimates an overall prevalence of ICA of 1:5,000-10,000.[4] One retrospective analysis of clinical visits for confirmed smell loss in children, revealed 67% with ICA.[3] While one series cites a high rate of congenital anosmia and head trauma among all anosmic children, a different study focused on patients with subjective rhinologic complaints finds sinonasal and obstructive etiologies as more common, demonstrating the impact of patient selection and inclusion criteria on study results.[5,24] A cross-sectional study found those with congenital anosmia had the worst thresholds among all etiologies, typically with no measurable olfactory function.[5]

In regards to evaluation and management of congenital anosmia, multiple studies have demonstrated the value of MRI with a relatively high rate of abnormalities identified.[24–27] The role of CT is less clear, but may be helpful to evaluate choanal atresia or nasal cavity hypoplasia.[27] Total anosmia, which is common to congenital anosmia, is associated with a worse prognosis for functional recovery. Olfactory event-related potentials can provide prognostic information in ICA.[28] Treatment remains challenging, with 0% of ICA patients in one series demonstrating improvement compared with 59.6% of post-viral patients.[29] There is some evidence that individuals with ICA and an intact olfactory pathway may demonstrate central perception of odorant stimuli on fMRI; and theophylline has been evaluated, although in a very low evidence study, to potentially have benefit for some of these individuals.[29,30,31] Most importantly, counseling on prognosis remains critical for setting expectations for individuals with ICA.

ICA is a rare condition with limited knowledge and data. Further well-designed studies will be required for a pooled analysis for more accurate characterization and identification of potential treatment options

Table VII.16 Section Evidence Summary Table: Related to congenital causes

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical Endpoint	Conclusion
Harris et al[5]	2006	2	Cross-sectional study	Outpatients with OD	Subjective and objective (ODT, OIT, SDOIT)	ICA and trauma present with poorest OD scores
Fonteyn et al[7]	2014	3	Retrospective cohort review (patients, single center)	Non-sinonasal OD	Subjective and objective (Sniffin' Sticks)	Total anosmia rate of 93.1% in ICA
Abolmaali et al[9]	2002	4	Case-control	ICA versus control subjects	MRI findings	Depth of olfactory sulcus on MRI reflects presence of olfactory tract

Aiba et al[26]	2004	4	Case series	Congenital anosmia subjects	MRI findings	MRI can identify abnormalities in patients with ICA
Croy et al[4]	2012	4	Case-control	ICA versus control subjects	Subjective (QoL questionnaires)	ICA associated with increased social insecurity, depression, accidents
Cui et al[28]	1997	4	Case-control	ICA versus control subjects	Smell Identification Test, ODT, ERP	Olfactory evoked potentials provide a measure of olfactory function
Dahmer-Heath et al[23]	2020	4	Case-control	Patients with renal ciliopathies	U-Sniff, Sniffin' Sticks	Underlying gene mutations (e.g. TMEM67) increases risk of hyposmia
Hauser et al[24]	2018	4	Case series	Pediatric patients with OD	Etiology, utility of imaging	MRI has higher utility than CT in evaluating ICA
Henkin et al[30]	2016	4	Non-controlled trial	ICA patients	Improvement in smell function on theophylline	Oral theophylline may restore olfactory function in some forms of ICA
Karstensen et al[11]	2018	4	Case-control	ICA patients versus controls	Objective (Sniffin' Sticks, MRI findings)	Characteristic relationship between volumetric MRI findings and OD
Kim et al[29]	2020	4	Retrospective cohort review	Patients with hyposmia	Objective (CCCRT test, CCSIT)	0% recovery for those with ICA
Leopold et al[13]	1992	4	Case series	Patients with presumed ICA	Objective (OCM), biopsies	ICA associated with abnormality or absence of olfactory neuroepithelium

Peter et al[12]	2020	4	Case-control	ICA patients versus controls	Objective (MRI findings)	Characteristic MRI findings with ICA
Powell et al[25]	2017	4	Retrospective case series	Patients with hyposmia	Objective (MRI findings)	ICA is rare (~5% of OD overall) and often presents in adulthood
Qu et al[27]	2010	4	Retrospective case series	ICA patients	Objective (T&T olfactometry, ERP, CT, MRI)	Total ansomia is most common in ICA, MRI can be helpful in diagnosis
Schriever et al[3]	2020	4	Retrospective case series	Patients with hyposmia	Chart review of etiology	2/3 of children with OD have ICA, but it becomes progressively less common into adulthood
Shushan et al[31]	2015	4	Case-control	ICA patients versus controls	fMRI with odor stimulus	fMRI activity in patients with ICA suggests odor may be subclinically perceived

OD = olfactory dysfunction

ICA = isolated congenital anosmia

ERP = event-related potentials

ODT = odor detection threshold

OIT = Odor Identification Test

SDOIT = San Diego Odor Identification Test

CCCRT = Connecticut Chemosensory Clinical Research Center

CCSIT = Cross-Cultural Smell Identification Test

OCM = Odorant Confusion Matrix

- **There are various congenital causes of smell loss.**

  Aggregate Grade of Evidence: C (Level 2 studies: 1, Level 3 studies: 1, Level 4 studies:15)

SECTION: VII. Pathophysiology

N. Related to extremely high or low Body Mass Index (BMI)

Anorexia nervosa (AN) and obesity may play a role in the pathogenesis of olfactory dysfunction (OD).

The literature evaluating the impact of extremely low BMI on olfactory function (OF) included one meta-analysis,[1] which concluded that OF is mainly intact in AN patients. One systematic review concluded that there might be alterations of OF in AN patients.[2] The current review summarizes all studies that measured OF in patients with extremely low BMI.

Most studies utilized the Sniffin' Sticks- TDI test.[3–14] While older studies showed significant heterogeneity of reported results and conclusions,[3,4,6–9,15–18] three recently published studies[5,13,14] provided further evidence that there might exist no relevant differences in olfactory function between AN and CO. Furthermore, those studies that concluded significant differences between AN and CO only showed marginal differences.[3,4,7–12,15,17,18]

The literature evaluating the impact of extremely high BMI on olfactory function (OF) included one systematic review that concluded solid evidence for a negative correlation between individual bodyweight and OF.[19] The current review summarizes all studies that measured OF in patients with extremely high BMI.

Most studies utilized the Sniffin Sticks TDI Test.[20–25] Eight studies showed greater OD risk among obese patients.[20,21,25–30] Five studies showed no relevant association between extremely high BMI and OD.[24,31–34] One study showed an age-dependent association between BMI and OF[35], and the remaining two studies reported about better OF in morbid obesity.[36,37]

One cross-sectional study revealed a positive correlation between correctly identified odors and BMI,[38] while the longitudinal study revealed no relevant association between BMI and OF.[39]

Two cross-sectional studies reported a higher OD-risk for MO patients.[40,41] Five interventional studies showed that OF improved significantly after bariatric surgery.[42–47] Two studies showed no effect of bariatric surgery on olfactory function.[48,49]

Table VII.16 Section Evidence Summary Table: Related to extremely low or high BMI							
	Author	**Year**	**LOE (1 to 5)**	**Study Design**	**Study Groups**	**Olfactory test method used**	**Conclusion**
Related to extremely high BMI							
	Guild[32]	1956	5	observational, cross sectional, case-control	Obese patients, n = 5 Control patients, n =5 all female	Blast injection method by Elsberg and Lewy	There was evidence that controls had greater olfactory acuity than obese patients
	Richardson et al[47]	2004	4	observational, cross sectional, case-control	Patients with BMI <45 = 47f/ 8m Patients with BMI > 45 = 40f/6m	12-item Cross-Cultural Smell Identification Test (CC-SIT)	Morbidly obese individuals are more likely than moderately obese individuals to demonstrate CC-SIT scores consistent with olfactory dysfunction
	Simchen et al[35]	2006	4	observational, cross sectional, case-control	Overweight patients, n = 87 Control patients, n = 226 Five age groups at intervals of 15 years with 50-60 participants each, all participants were ≥20 years	European test of olfactory capabilities (ETOC)	Age-dependent association between BMI and olfactory function: odor detection and identification function were lower in overweight than in control when the age was <65 years, whereas in subjects ≥65 years, functions were better in overweight than in control
	Trellakis et al[33]	2010	4	observational, cross sectional, case-control	Obese patients, n = 12 Control patients, n = 10	Sniffin Sticks TDI Test	No significant difference in overall olfactory function was observed in relation to BMI

					Overweight patients, n = 9		
	Zijlstra et al[34]	2011	4	observational, cross sectional, case-control	Overweight/Obese. n = 21f/6m Control patients, n = 21f/6m	Retro-nasal aroma release using spiced rice	There were no significant differences in recognition of retro-nasal aroma release between the groups
	Skrandies et al[20]	2015	3b	observational, cross sectional, case-control	Obese patients, n = 7 Overweight patients, n = 18 Control patients, n = 30 Low Weight patients, n = 5	Sniffin Sticks TDI Test	Higher BMI was associated with worsened odor threshold function
	Stafford and Whittle[36]	2015	4	observational, cross sectional, case-control	Obese patients = 9f/11m Control patients = 15f/5m	Olfactory threshold test based on dark chocolate odorant	Obese individuals were better at detecting the chocolate odor compared with the nonobese group.
	Fernandez-Aranda et al[21*]	2016	3b	observational, cross sectional, case-control	Obese patients, n = 59 Control patients, n = 36 all female	Sniffin Sticks TDI Test	Overall olfactory function was clearly impaired in the obese compared to the control group

	Fernandez-Garcia[25*]	2017	3b	observational, cross sectional, case-control	Morbidly obese patients, n = 46 Obese patients, n = 28 Overweight patients, n = 12 Control patients, n = 77, Low Weight patients, n = 17, all female	Sniffin Sticks TDI Test	Obese patients had significantly lower overall olfactory function compared to the control group
	Uygun et al[28]	2019	3b	observational, cross sectional, case-control	Obese patients, n = 52 Control patients, n = 15years all female	Sniffin Sticks 12-item Identification Test+CCCRC Butanol threshold	Obese women had lower odor identification function compared to the control group
	Zhang et al[29†]	2019	3b	observational, cross sectional, case-control	Obese patients = 15f/20m Control patients = 15f/20m	OLFACT	Obese subjects had lower olfactory threshold function compared to the control group
	Besser et al[26]	2020	3b	observational, cross sectional, case-control	Obese patients = 11f/4m Control patients = 47f/27m	Sniffin Sticks TDI Test	Overall olfactory function declined with rising BMI
	Herz et al[23]	2020	3b	observational, cross sectional, case-control	Obese patients = 12f/15m Control patients = 12f/14m	Sniffin Sticks TDI Test	Adolescents with a higher BMI had higher ofactory threshold function compared to the control group

	Poessel et al[31]	2020	3b	observational, cross sectional, case-control	Obese patients = 14f/14m Overweight patients = 5f/6m Control patients = 14f/14m	Sniffin Sticks TDI Test	There was no statistically significant difference between weight groups with regard to measured olfactory function
	Poessel et al[24]	2020	3b	observational, cross sectional, case-control	Obese patients = 11f/13m Overweight patients = 12f/13m Control patients =14f/12m	Sniffin Sticks Threshold Test	No statistically significant difference between Obese, Overweight, and Control subjects regarding odor thresholds
	Nettore et al[30]	2020	4	observational, cross-sectional, case control	Obese patients = 92f/48m Overweight patients = 92f/48m Control patients = 92f/48m	Flavor identification test consisitng a series of 20 aromatic extracts and one blank	The BMI inversely correlated with the number of correctly identified flavors. The number of correctly identified flavors was significantly higher in control patients compared to obese patients
	Boesveldt et al[38]	2011	4	observational, cross sectional, population-based	Population = 1550f/1455m, mean age = 69.3 mean BMI = 29.1 (range 14.1 -75.6)	Sniffin Sticks 5-item Identification Test	There was a positive correlation between correctly identified odors and BMI
	Liu et al[39]	2020	3b	observational, longitudinal, population-based	BMI < 25 kg/m², n = 761 BMI 25-30 kg/m², n = 970 BMI > 30 kg/m², n = 558 1189f/1110m mean age of all participants = 75.6 years	Brief Smell Identification Test	At baseline, BMI was not associated with poor olfaction. Poor olfaction was associated with older age, male sex, black race, lower education level, alcohol drinking, smoking, and fair to poor health status.

	Obreowski et al[41]	2000	4	observational, cross-sectional, case series	Obese patients, 15f/15m	Blast injection method by Elsberg and Lewy	Obese children had significantly lowered thresholds of detection and of identifying odors compared to normative data
	Richardson et al[48]	2012	4	intervention, cohort study	Morbidly obese patients = 50f/5m Control patients = 32f/8m	Cross-Cultural Smell Identification Test	Larger percentage of morbidly obese patients scored within the olfactory dysfunctional range compared to the control group. Gastric bypass surgery did not influence olfactory function
	Enck et al[49]	2014	3b	intervention, cohort study	Morbidly obese patients = 4f/4m Control patients = 22f/22m	Sniffin Sticks TDI Test	Obese patients had significantly lower overall olfactory function compared to the control group. Bariatric surgery did not change odor sensitivity.
	Jurowich et al[42]	2014	3b	intervention, cohort study	Morbidly obese patients = 29f/13m Patients were divided into three groups according to the surgery that they received	Sniffin Sticks TDI Test	The morbidly obese group with the highest mean BMI had the lowest overall olfactory function. Those that received sleeve gastrectomy surgery improved significantly postoperatively.
	Holinski et al[43]	2015	3b	intervention, cohort study	Morbidly obese patients = 29f/15m Control patients = 15f/8m	Sniffin Sticks TDI Test	Obese patients had significantly lower overall olfactory function compared to the control group. In morbidly obese patients, olfactory function increased significantly after laparoscopic bariatric surgery

	Hanci et al[46]	2016	3b	intervention, cohort study	Obese patients = 32f/22m	Sniffin Sticks TDI Test	Median score of obese patients was within the olfactory dysfunctional range compared to normative data. Olfactory function increased signficantly after laparoscopic sleeve gastrectomy
	Zerrweck et al[44]	2017	4	intervention, cohort study	Morbidly obese patients = 16f/5m	Pocket Smell Test	The probability of having severe or total anosmia in obesity is extremely low. Olfactory function increased signficanlty after laparoscopic gastric bypass surgery
	Campolo et al[47]	2020	4	observational, cross-sectional, case series	Obese patients = 31f/29m	Sniffin Sticks TDI Test	Among middle-aged subjects with stage I and II obesity, olfactory dysfunction was highly prevalent with respect to normative age- and gender-adjusted cut-offs
	Melis et al[45]	2021	4	intervention, cohort study	Patients undergoing bariatric surgery = 36f/15m	Sniffin Sticks 16-item Identification Test	The olfactory function of participants improved after bariatric surgery.
	Peng et al[19]	2018	2		10 obervational studies and 9 longitudinal studies		Strong evidence for a link between olfaction and obesity. Bariatric surgery might reverse obesity related olfactory decline.
Related to							

extremely low BMI							
	Fedoroff et al[15]	1995	4	observational, cross sectional, case-control	AN patients, n = 11 C patients, n = 16 all female	UPSIT + Odor detection threshold	Very low weight AN patients showed impairments in their ability to identify and detect odors
	Kopala et al[16]	1995	3b	observational, cross sectional, case-control	AN patients, n = 27 C patients, n = 50 all female	UPSIT	No relevant difference in olfactory function between the AN and C groups
	Smoliner et al[6]	2013	4	observational, cross sectional, case-control	cohort = 137f/54m 4 patients had a BMI < 20 kg/m²	Sniffin Sticks 12 item Identification Test	No association between nutritional status and olfactory dysfunction in geriatric patients
	Lombion-Pouthier et al[17]	2005	4	observational, cross sectional, case-control	AN patients, n = 17 C patients, n = 58 all female	Test Olfactif	AN patients had higher olfactory sensitivity compared to the C group
	Roessner et al[3]	2005	4	observational, cross sectional, case-control	AN patients, n = 17 C patients, n = 15 all female	Sniffin' Sticks TDI test	AN patients had lower odor threshold and discrimination function compared to the C group
	Schreder et al[4]	2008	3b	observational, cross sectional, case-control	AN patients, n = 12 C patients, n = 24 all female	Sniffin' Sticks TDI test	AN patients had lower overall olfactory function compared to the C group
	Aschenbrenner et al[7]	2009	3b	observational, cross sectional, case-control	AN patients, n = 16 C patients, n = 23 all female	Sniffin' Sticks TDI test	Overall olfactory function was lower in AN patients compared to the C group
	Rapps et al[8]	2010	3b	observational, cross sectional, case-control	AN patients, n = 19 C patients, n = 21 all female	Sniffin' Sticks TDI test	Odor identification function was lower in AN patients compared to the C group

	Schecklmann et al[9]	2012	3b	observational, cross sectional, case-control	AN patients, n = 26 C patients, n = 23 all female	Sniffin' Sticks TDI test	Odor identification function was higher in AN patients compared to the C group
	Stein et al[18]	2012	4	observational, cross sectional, case-control	AN-R patients, n = 40 AN-BP patients, n = 23 C patients, n = 20 all female	Bottle threshold and discrimination test	AN patients had higher odor discrimination but lower threshold function compared to the C group
	Dazzi et al[10]	2013	4	observational, cross sectional, case-control	AN patients, n = 18 C patients, n = 19 all female	Sniffin' Sticks TDI test	Overall olfactory function was higher in AN patients compared to the C group
	Fernández-Aranda et al[11*]	2016	3b	observational, cross sectional, case-control	AN patients, n = 64 C patients, n = 80 all female	Sniffin' Sticks TDI test	Overall olfactory function was higher in AN patients compared to the C group
	Bentz et al[12]	2017	3b	observational, cross sectional, case-control	AN patients, n = 43 C patients, n = 39 all female	Sniffin' Sticks Threshold and Identification test	AN patients had higher olfactory sensitivity 149ompared to the C group
	Fernandez-Garcia al[13*]	2017	3b	observational, cross sectional, case-control	LW patients, n = 17 C patients, n = 77 all female	Sniffin' Sticks TDI test	No relevant difference in olfactory function between LW and C groups
	Tonacci et al[13†]	2019	3b	observational, cross sectional, case-control	AN patients, n = 19 C patients, n = 19 all female	Sniffin' Sticks TDI-extended Identification test	No relevant difference in olfactory function between the AN and C groups

	Kinnaird et al[5]	2020	3b	observational, cross sectional, case-control	AN patients, n = 38f/2m C patients, n = 38f/2m	Sniffin' Sticks TDI test	No relevant difference in olfactory function between the AN and C groups
	Islam et al[2]	2015	3a	systematic review	14 studies		The findings do indicate alterations of smell capacity in AN patients
	Mai et al[1]	2020	1	systematic review and meta-analysis	14 studies		Olfaction was largely intact in AN compared to C patients.

- **Extremely low body weight is not associated with increasing OD risk.**
  `Aggregate Grade of Evidence: B (Level 3: 1 study, Level 3b: 10 studies, Level 4: 6 studies)

- **Extremely high body weight increases OD risk. Weight loss might reverse OB-related OD.**
  Aggregate Grade of Evidence: B (Level 2: 1 study, Level 3b: 14 studies – Level 4: 12 studies, Level 5: 1 study)

SECTION:VII.16 Pathophysiology

O. Related to smoking

Chronic cigarette smoking may contribute to olfactory dysfunction (OD) pathogenesis. Literature evaluating chronic smoking on olfactory function (OF) includes a meta-analysis, concluding that current (but not necessarily former) smoking associated with 59% greater OD risk (Ajmani et al).[1] Additional studies are reviewed below and in **Table VII.17**

All interventional studies with measured olfaction showed OF improvement with smoking cessation, nasal irrigation, and nasal polyp surgery for smokers with post-surgery smoking cessation.[2–5]

One longitudinal study showed reversal of smoking-mediated OD, although OD may persist years after smoking cessation. The other longitudinal study reported current smoking to be associated with greater OF decline.[6,7]

A nationally representative cross-sectional study showed that ever versus never smokers had significantly lower OD risk and the other nationally representative cross-sectional study did not show a significant relationship between smoking and OD.[8,9]

Nine population based studies showed greater OD risk among smokers, and two did not.[10–20]Of community based studies, six studies showed greater OD risk among smokers; one demonstrated dose-response relationships. Two only included participants who denied OD or OD-associated problems and failed to find significant smoking-OD risk associations.[21–28]

When looking at cross-sectional studies with self-rated olfaction, a larger U.S. dataset revealed significant smoking-OD associations, partially-mediated by olfactory-related conditions. In Korean adults with chronic rhinosinusitis (CRS), smoking was associated with CRS but not OD.[29–31] Another non-representative population based study showed no significant smoking-OD associations.[32], but a community based study showed significant smoking-OD associations.[33]

Six clinical studies with measured olfaction showed an association between smoking and OD, with one additional study finding significant smoking-OD associations only in patients with post-traumatic OD.[34–40]

2 peri-operative studies in the context of post-coronary artery bypass graft, and post-endoscopy sinus surgery found smoking to be associated with post-operative OD.[35,4] In two studies, CRS smokers had greater risk of OD, particularly those with eosinophilic-CRS.[38,39]

In Parkinson's disease patients a case-control analysis found greater risk of OD in smokers and lower risk in smokers with PD. In the other, first-degree, non-smoker relatives of PD patients showed non-significant smoking-OD risk associations.[36,37]

One observational study of patients seen in an ENT outpatient clinic reported smokers had higher risk of OD.[41]

Two studies found worse OF in smokers (versus non-smokers), one reported temporal associations between smoking and reduced nasal pungency, whereas one found no difference in retronasal perception in smokers. One study reported that swallow-related muscle

compensation was associated with worse OF in smokers, another reported lower olfactory bulb volume in smokers. One reported better OF with brief (16-20 hours) abstinence from smoking.[42–48]

Table VII.17 Section Evidence Summary Table: Related to smoking							
Author	Year	Design	LOE (1 to 5)	Study Group	Olfactory indicator	Smoking Measure	Conclusion
Dinc, et al.[2]	2020	Prospective cohort - Intervention	2	28 volunteers who were admitted to smoking cessation section program and with chemosensory-related conditions. Average 22 cigarettes/day.	"Sniffin'Sticks" extended (odor threshold, odor discrimination, and odor identification) immediately before smoking cessation and 45 days after smoking cessation.	Cigarettes/day and years smoking.	Improvement in measured olfactory function as soon as 45 days after smoking cessation, with more improvements in those who had smoked for the fewest years prior to cessation.
Ottaviano et al.[3]	2012	Prospective, randomized, double-blind study	2	70 consecutive smokers (18 to 65 years) diagnosis of nonallergic chronic rhinitis, and cigarette smoking habit for ≥5 years. Nonallergic chronic rhinitis, based on clinical evidence, nasal resistances, cytology, and	Butanol olfactory threshold test with Sniffin' Sticks test	Cigarettes/day and years smoking.	Simple, isotonic sodium chloride solution nasal irrigations significantly improved their olfactory threshold.

				olfactory thresholds			
Danielides et al.[4]	2009	Prospective cohort	2	Smokers consisted of 22 men and 22 women (mean age=46 years) who averaged 20 cigarettes smoked/day. Excluded were patients who were past smokers, normosmics (by testing), and those refusing to quit smoking after surgery.	Sniffin' Sticks extended (odor identification, discrimination, threshold) at baseline, 1, 3, and 6 months in a bilateral mode	Pack-years (number of packs smoked per day, number of years of smoking)	Both smokers and nonsmokers with massive nasal polyps presented a highly significant improvement in olfactory function during the 6-month postoperative period after ESS, provided that all smokers quit smoking after surgery. Heavy smoking was associated with poorer olfactory thresholds.
Etter et al.[5]	2013	RCT	2	Adult daily smokers (n=1126) and former smokers (n=3239). Daily smokers were assigned randomly to continue smoking	Self-reported smell and taste from 'very poor' to 'verygood'	Revised Minnesota Withdrawal Scale (MWS-R). Cigarettes/day	Smokers who abstained from smoking reported improvements in the sense of smell right after quitting as well as improved

				for 2weeks or to stop smoking. Occasional smokers and never smokers were excluded.		and years smoking.	sense of taste and sore throat.
Siegel et al.[6]	2019	Population survey case series	4	3,528 older adults, including 1,526 former smokers	Sniffin' Sticks (5-Odor identification test)	Non-smokers, former smokers (asking age started smoking regularly, age quit, number of cigarettes smoked on average per day), current smokers (age started, number of cigarettes on average day)	Smoking-mediated olfactory dysfunction is reversible but may persist for 15 years after smoking cessation. Former smokers who had quit within 15 years had significantly impaired olfaction compared to never smokers, but those who quit more than 15 years ago had similar olfaction as never smokers.

Schubert et al. [7]	2015	Prospective cohort	2	3,296 participants (ages 21–84 years) in the baseline BOSS (2005–2008), and 2,792 (84.7%) of them, plus an additional 80 people who were unable to participate in the baseline phase	San Diego Odor Identification Test	Current, former, or never	Current smoking (versus never smoking) was associated with increased risk of olfactory decline
Hoffman et al.[8]	2016	U.S. Nationally-representative, cross-sectional	4	1818 NHANES participants aged ≥40 years, 1281 (70.5 %) completed the exam	Odor identification task (Pocket smell test; 8-item)	Current, ever, never smoker	Smoking was not identified as a risk factor for olfactory dysfunction; the logistic regression unexpectedly showed that past smoking, after adjusting for age and sex, was associated with decreased risk of olfactory dysfunction.
Pinto et al.[9]	2014	Cross-sectional survey	4	N=3005, with oversampled African Americans, Hispanics, men, and the oldest participants	Sniffin sticks (5-odor identification task)	Current smoking, based on either salivary cotinine level (n	Smoking did not explain the worse olfactory function in African Americans and Hispanics, who

						= 2,219) or self-report (n = 709)	had markedly worse olfactory function (controlling for gender and age) compared with whites. In re-analysis of these data (Ajmani et al, 2017, see below), smoking did not associate significantly with the odds of olfactory dysfunction.
Jalali et al.[10]	2020	Population-based cross-sectional study	4	1470 participated; reasonably representative of the population of individuals without self-reported loss of smell or taste or related diseases and treatments	Iran Smell Identification Task	Previous history of smoking, smoking dose (pack-years). A cigarette pack-year was defined as a pack of cigarettes (20 cigarettes) smoked	Olfactory dysfunction frequency in smokers (22.5%) was significantly more frequent than in former (19.8%) and non-smokers (13.2%). There was a significant negative association between total scores of Iran-SIT and the total number of cigarettes.

						every day for one year.	
Fluitman et al.[11]	2019	Cross-sectional analysis within a cohort study	2	824 Dutch community-dwelling older adults from the ongoing Longitudinal Aging Study Amsterdam (LASA)	40-item University of Pennsylvania Smell Identification Test (UPSIT; same as SIT)	Smoking status was dichotomized into non-smokers (never or former smoker) and current smoker. For current smokers, the number of cigarettes per week was documented	Significant difference in median UPSIT-score between never smokers and current smokers and between former smokers and current smokers, but not between former smokers and never smokers (33 versus 33, adjusted p=1.000). No difference in the number of cigarettes smoked/week by categories of normosmic, microsmic and anosmic. Lower olfactory function scores were associated with lower BMI in older adults

							who smoke, but not in older adults who do not smoke.
Khil et al.[12]	2015	Cross sectional study	2	Random sample of 3820 inhabitants aged 25 to 74 years from the population register of Dortmund, a city in western Germany.	Sniffin' Sticks–Screen (12-set odor identification)	Smoking status (never, former smoker, current smoker)	Current smoking was significantly associated with greater odds of olfactory impairment.
Schubert et al.[13]	2012	Population-based cross sectional study	2	2838 participants, 1293 (45.6%) men and 1545 (54.4%)	San Diego Odor Identification Test (8 odors) and related olfaction questions. 'Do foods you eatnow taste as good as when you were younger?'' and ''Doyou experience food flavors (e.g.,	Smoking history (ever smoked 100 cigarettes or more), exposure to environmental tobacco smoke at home, work, and in social	History of smoking was associated with an increased odds of olfactory impairment in women only (ever smoked vs. never smoked).

					chocolate, vanilla) thesame as you used to''	situations	
Doty et al.[14]	2011	Population-based cohort	2	Two Danish nationwide population-based surveys (Longitudinal Study of Aging Danish Twins; Danish 1905-Cohort 2005 survey); 91 centenarians (18 men, 73 women); 1,131 elderly twins (513 men, 618 women)	12-odorant Brief-Smell Identification Task (B-SIT)	Never, past, current	Smoking explained significant variability in odor identification ability in multiple regression analysis.
Ranft et al.[15]	2009	Prospective cohort study	2	402 older adults who lived at the same address for 20 years	Sniffin' Sticks–Screen (16-set odor identification)	Nonsmokers (n=388); former smokers (15%); passive smoker (40%)	No effects of smoking on odor identification.
Vennemann et al.[16]	2008	Cross sectional population survey	2	1312 participants (randomly drawn) within 5-year age groups (25 to 75	Sniffin' Sticks for odor	Current smokers, ex-smokers,	Current smokers had greater risk for smell impairment

				years), stratified by gender	identification (12 odors)	nonsmoker	(adjust odds ratio). There was a dose response relationship between increasing number of daily smoked cigarettes and smell impairment. Former smoking was not related to smell impairment.
Murphy et al.[17]	2002	Population-based cross sectional study	2	43 to 84 years (mean age=69) in 1987-1988, residence of Beaver Dam in 1987-1988, 2800 participants (did not exclude dementia but less likely to participate in olf testing).	San Diego Odor Identification Test and related olfaction questions. Do you have a normal sense of semll (compared to other people)?	Current, former, never smokers	Current vs never smokers had 93% greater odds of olfactory dysfunction
Veyseller et al.[18]	2014	Case control	4	426 healthy volunteers without otolaryngologic condition causing olfactory	Connecticut Chemosensory Clinical Research Center (CCCRC)	Smokers vs non-smokers	Smokers averaged significantly lower CCCRC scores (threshold, odor

				dysfunction (measured or self-reported)	olfactory test (butanol threshold, 8 odor identification task)		identification) than non-smokers.
Liu et al.[19]	1995	Cross-sectional	4	510 subjects (≥50 years old; 239 men, 271 women)	12 odor identification test	Ever smoker, non-smoker.	Smoking status (ever) had independent effects on odor identification in multiple regression analysis.
Mackay-Sim et al.[20]	2006	Cross sectional	4	485 healthy, nonmedicated, nonsmokers with no history of nasal problems and 457 who were either medicated, smokers or had a history of nasal problems	Sniffin' Sticks (olfactory threshold, olfactory discrimination, and olfactory identification)	Smokers versus nonsmokers	No effects of smoking on olfactory function, although most smokers were less than 40 years old (suggested less exposure to smoking)
Ishimaru et al.[21]	2007	Cross-sectional	2b	557 Japanese adults (368 men and 189 women)	Cross-cultural smell identification test	Brinkman Index (BI: number of cigarettes consumed per day	Smokers and previous smokers had lower olfactory function than non-smokers.

						multiplied by years of smoking) and urine test for nicotine intake level.	
Frye et al.[22]	1990	Cross-sectional	2b	638 employees (553 males, 85 females; mean age=43 year) of a large chemical manufacturing facility. 260 never smokers, 197 former smokers, 170 current smokers	40-odorant UPSIT/SIT	Pack-Years	Current smokers are nearly twice as likely to have an olfactory deficit than persons who have never smoked (adjusted odds ratio). No elevated risk of olfactory dysfunction was found for previous smokers when compared with never smokers. There was a dose relationship between pack years and decreased odor

							identification ability.
Doty et al.[23]	1984	Cross-sectional	2b	1339 volunteers (ages 10 to 99) without reported smell abnormalities and who were able to correctly identify at least half of the odorants	40-odorant UPSIT/SIT	Smokers, nonsmokers	Current smoking was associated with lower odor identification ability, but the effects were not large and not in a dose relationship.
Delgado-Losada et al.[24]	2020	Cross-sectional	4	209 healthy normosmic volunteers (without any conditions associated with olfactory dysfunction)	Sniffin' Sticks extended olfactory test (olfactory threshold, olfactory discrimination, olfactory identification, and combined)	Self-reported smokers vs non-smokers	No differences in olfactory dysfunction between smokers and non-smokers.
Nettore et al.[25]	2020	Cross-sectional	2b	348 subjects (F = 241, M = 107), with a mean age of 42.41 ± 15.63 years who did not report a smell or taste problem. 25% of sample	Flavor identification task of 20 flavors. Subjective chemosensory function, namely	Non-smokers (never smoked; smoking cessation >10 years	Cigarette smoking did not seem to influence flavor recognition; were able to see age and

				smoked, averaging 10.52 ± 8.20 cigarettes/day, and 15.15 ± 12.77 years.	flavor ("How would you rate your fine taste, e.g., during eating and drinking?") on a visual analogic scale.	previously) versus current (number of cigarettes per day, number of years smoking).	female/male differences.
Duffy et al.[26]	2019	Case-control analysis	4	135 chronic smokers; For nicotine dependence, 84% reported smoking within 30 minutes of waking.	16-item odor identification (generated by a portable olfactometer) task and intensity rating. Self-rated smell alteration following NHANES protocol.	Participants completed the Fagerstrom Test of Nicotine Dependence, including time to first cigarette and the Wisconsin Inventory of Smoking Dependence Motives.	Approximately 41% of the smokers had measured olfactory dysfunction, primarily hyposmia, which was up to 7-fold higher than the non-smokers from 2013-2014 NHANES. Awareness of the problem among those with measured dysfunction (sensitivity of self-report) was low.

Katoto et al.[27]	2007	Cross-sectional, observational	3	114 healthy volunteers—57% were smokers and 43% had never smoked with no passive smoke exposure. Nasal endoscope and CT scan confirmed to no abnormal nose and the paranasal sinuses. No history of any major olfactory disturbance.	"Sniffin' Sticks" for threshold, recognition and identification	Pack-years	Smokers had significantly lower function for olfactory identification, detection and threshold, even controlled for age and gender in multivariate regression and logistic analysis, and treating pack-years as a continuous variable.
Cardesín et al.[28]	2006	Cross-sectional	4	120 healthy volunteers without subjective olfactory disturbances (January 2001 to February 2003)	24-item odor identification task	Smokers vs non-smokers	Smokers scored lower on odor identification for some odors.
Glennon et al.[29]	2019	Cross-sectional	2	Adults 40+ years; NHANES 2011-2014 (n = 7418) participants (mean age = 57.8 ± 12.2 years). Nearly half of the sample were former/current smokers (47.4%).	NHANES self-rated based on a score of three questions (olfactory problems in the past years; worse ability since	Self-reported by chronicity (pack years, PY) and dependency (time to first cigarette	Estimated prevalence of altered olfaction was 22.3%, with age-related increases. ≥10 PY smokers had significantly greater odds of altered olfaction versus never

					age 25; phantom smells).	upon waking) and verified by serum cotinine. Smoking (never, former, current)	smokers; greater odds among current smokers (≥10 PY) who also had high nicotine dependence (smoked ≤30 min of waking). Light smokers (≤10 PY smokers) did not show increased odds versus never smokers. Current smokers who also were heavy drinkers (≥4 drinks/day) had the highest odds for altered olfaction (OR 1.96, CI: 1.20-3.19). Olfactory-related pathologies (sinonasal problems, serious head injury, tonsillectomy, xerostomia) partially mediated the association

							between smoking and altered olfaction.
Rawal et al.[30]	2016	Cross-sectional	4	3603 adults, ages ≥40 years, who answered the CSQ (response rate 99.9%)	NHANES self-rated based on a score of three questions (olfactory problems in the past years; worse ability since age 25; phantom smells).	Smoking exposure was categorized as none (never smoked 100 cigarettes), <10 pack years (PY, packs of cigarettes smoked per day × years smoked), and ≥10 PY.	Logistic regression, ≥10 PY was not a significant predictor of self-reported smell alteration in adjusted logistic regression models.
Lee et al.[31]	2015	Cross-sectional	4	1,589 adults completed questionnaires on rhinologic symptoms and smoking behaviors and	"Have you had problems with your sense of smell during	Active smokers, passive smokers, and nonsmokers	The odds of self-reported olfactory dysfunction did not vary significantly in active smokers

				underwent nasal endoscopy. Chronic rhinosinusitis diagnosis from 2 or more symptoms, including olfactory dysfunction	the past 3 months?"	based on questionnaire responses and urine cotinine levels.	versus passive or nonsmokers in adjusted logistic regression (in younger ≥19 years or older ≥40 years). Total smoking period (years) was significantly associated with CRS, not other smoking behaviors (age started, number of cigarettes/day, pack-years of smoking).
Huang et al.[32]	2017	Cross-sectional	4	12,627 Chinese participants (10,418 men and 2209 women; mean age: 54.4 y) who did not take hypolipidemic agents	National Health Interview Survey—''Do you have any problems with your sense of smell, such as not being able to smell things or things not smelling the way they	Never, past, current smokers	There were no significant differences in smoking status by chemosensory categories (no taste or smell problem, smell or taste dysfunction, smell and taste dysfunction). Significant association between

					are supposed to for ≥3 mo?''		chemosensory dysfunction and a higher concentration of TC, particularly among younger adults and nonsmokers.
Collins et al.[33]	1999	Cross-sectional	2	144 volunteers, including 60 smokers (22 men, 27 women), 61 nonsmokers (19 men, 42 women), 23 passive smokers (5 men, 18 women)	Self-reported (Has your sense of smell become reduce) on a visual analog scale.	Smoker, nonsmoker, passive smoker, non-smoker (never, not smoking >5 years)	Smokers were four times and the passive smokers six times more likely to report a diminished sense of smell than the non smokers.
Fjaeldstad et al.[34]	2021	Retrospective observational study	4	3,900 patients with olfactory loss; 521 patients were current smokers, and 316 patients had a history of smoking	Sniffin' Sticks extended olfactory test (olfactory threshold, olfactory discrimination, olfactory identification, and combined)	Smoking dose was calculated in pack-years (packs smoked perday multiplied with number of years where smoking	No significant overall differences in measured olfaction between current, former and nonsmokers; adults with posttraumatic olfactory loss were significantly more likely to be current smokers.

						occurred).	
Erdem et al.[35]	2019	Prospective, pre- and post-operative study	2b	60 patients post-CABG (first time) divided into 30 Off-Pump and 30 On-Pump CABG groups	Brief Smell Identification Test (B-SIT; 12 odors)	Smoking - yes/no	Smokers had lower olfactory function pre-operatively and post-operatively.
Sharer et al.[36]	2015	Case control analysis	4	323 PD patients and 323 controls closely matched individually on age, sex, and smoking history (never, past, or current)	UPSIT/SIT	Never, past, current smoker	In controls, smokers had significantly lower odor idenitification scores; current PD smokers had higher odor identification that former or never smokers.
Siderowf et al.[37]	2007	Observational	4	173 first-degree relatives (>50 years old; within 10 years of the age of PD onset), free of conditions that could affect olfactory function; excluded current smokers	UPSIT/SiT	Never smokers (1 to 10 lifetime pack-years) and greater than 10 pack-years	Nonsignificant association between former smoking status and olfactory performance.

Mori et al.[38]	2013	Multicenter prospective cohort study	2b	418 patients with preoperative olfactory data by eosinophilic (ECRS) or non eosinophilic chronic rhinosinusitis (NECRS)	olfactometry and an intravenous olfactory test (garlic odor). Detection and recognition thresholds for 3 odorants: b-phenylethyl alcohol, cyclotene , and isovalericacid.	Past, current, non-smokers	Current smoking was a risk factor for ECRS; olfactory dysfunction was more severe and more prevalent in patients with ECRS than in patients with NECRS.
Litvack et al.[39]	2008	Multi-institutional cross-sectional analysis	2b	396 subjects with diagnosis of CRS recruited from three tertiary care centers over a three-year period	UPSIT/Smell Identification Test (SIT; 40 odors)	Current tobacco use	Current smokers were at increased odds of anosmia as compared to patients under 65 years, without nasal polyposis, non-asthmatics and non-smokers.
Sugiyama et al.[40]	2002	Case series	4	37 patients (30 men, 7 women; mean age 43 years) who underwent functional	UPSIT/SIT	Pack-years	Significant correlation between greater pack-years and lower post-op olfactory

				endoscopic sinus surgery. 13 (35.1 %) were cigarette smokers; 18 had undergone previous surgical intervention for their nasal disease.			function in a population with high levels of smoking.
Şanlı et al.[41]	2016	Case series	4	1,840 randomly selected patients (823 males, 1,017 females), >25 years old, admitted to ENT outpatient clinic over 1 month (March, 2014)	Self-reported "taste" disorders and smell disorders	Smokers (≥10 cigarettes/day for ≥five years; n=514); Ex-smokers (no smoking for ≥1 year after ≥5years of smoking; n=268). Never smokers (n=1,058). Passive smokers excluded .	Nasal congestion, smell disorders and snoring were significantly higher in smokers; symptoms such as runny nose, sneezing, nasal discharge and headache were close to the control group. All symptoms were found to be significantly lower in ex-smokers.

Pepino et al.[42]	2014	Case-control	4	14 obese smokers, 11 obese never-smokers, 10 normal-weight smokers, 12 normal-weight never-smokers	Retronasal olfaction - nose plugged and then unplugged during sampling of vanilla pudding for sweetness, creaminess and hedonic intensity ratings	Number of years smoking, number of cigarettes/day, age smoking started and then regular smoking	Co-occurrence of smoking and obesity is significantly associated with reduced perception and hedonic value of dessert-type sugar/fat mixtures; more decline of creaminess than retronassal olfaction.
Santos et al.[43]	2014	Case control	4	24 smokers and 24 who had never consumed tobacco, gender and age matched. Smokers were under outpatient pulmonary care.	Smell diskettes odor identification task	Current smokers	Odor ID score averaged lower in smokers vs. non-smokers related to muscle compensation during swallowing.
Schriever et al.[44]	2013	Case control	4	21 smokers (9 men, 12 women; mean age= 22.5 year) and 59 non-smoking control subjects (23 men, 26 women; mean age=23.9 years) matched for gender and age	Odor thresholds for phenylethyl alcohol	Smokers ≥3 cigarettes/day for average duration of smoking was 7.5 years. Former	Average threshold for PEA did not differ by smoking status; odor ID trended to be lower in smokers. Smokers had significantly lower OB volume

						smokers were recent quitters (had quit for 0–31 days) and long-term quitters (had quit for 91+days, not analyzed further). Abstinence or relapse were having smoked (or not) in the previous 24 hours.	than did non-smokers. There was no significant correlation of duration of smoking with OB volume. Uncertain if quitting smoking reverses association OB volume differences.
Hayes et al.[45]	2012	Case control	4	23 nonsmokers (10 males and 13 females; mean age: 25 years) and 23 smokers (11 males and 12 females; mean age: 24 years). Smokers averaged	Olfactory threshold for n-butanol and PEA	Pack years (amount, years)	Smokers had higher olfactory detection thresholds, including greater pack years and higher thresholds.

				8 cigarettes/day for an average of 5 years or 2.4 pack years. Nonsmokers did not have dsecond hand smoke exposure or were former smokers			
Rosenblatt et al. [46]	1998	Case-control	4	Twenty volunteer patients of a Veteran's Affairs Medical Center	Nicotine threshold was tested first followed by menthol testing.	Smokers (smoking at least half a pack of cigarettes per day for at least the last 10 years). Ten subjects were nonsmokers. Smoking status was confirmed by end-expired carbon monoxide.	Current smokers had higher olfactory threshold that is reduced with an experimental abstinence.

Ahlström et al.[47]	1987	Case control	4	67 adults (32 men, 35 women; ages 19 to 43 years)—26 smokers (14 men, 12 women), 26 nonsmokers [13 men, 13 women), 15 passive smokers (five men, 10 women)	Six concentrations (pyridine and n-butane) from perceptually weak to moderately strong odors	Smokers, non-smokers, passive smoke exposure	Smokers reported lower intensities than do nonsmokers, across all concentrations.
Cometto-Muñiz et al.[48]	1982	Case conntrol	4	21 smokers (7 males, 14 females; average age, 25 years; average daily consumption, 15 cigarettes for 9 years) and 20 nonsmokers (6 males, 14 females; average age, 25.1 years)	Perceived intensity (magnitude matching) of irritation, odorant, and tone	Smokers vs. nonsmokers	Smokers perceive nasally inhaled common chemical stimuli less keenly than nonsmokers. Short periods of smoking further impair the smoker's sensitivity to an irritant. The odor intensity wasn't different rather the pungency.
Ajmani et al.[1]	2017	Meta-analysis of observational studies between 1970–2015	1	7 studies included 11,771 subjects (highlight in orange above)	Odor identification	Current, former, never	Pooled analysis showed that smoking was associated with a 59% increased odds of olfactory dysfunction. Significantly

							increased odds of olfactory dysfunction was not seen in former smoker than never smokers.

- **Cigarette smoking increases risk of OD. Former smokers may recover OF, although length of smoking may influence recovery.**
  Aggregate grade of evidence: B (Level 1: 1 study, Level 2: 21 studies, Level 3: 1 study, Level 4: 24 studies)

SECTION: IX. Pathophysiology

O. Idiopathic

Idiopathic olfactory dysfunction (IOD), by definition, is without an identified cause despite a comprehensive workup. Likewise, little is known regarding the pathophysiology of IOD, despite this clinical entity accounting for up to one sixth of patients with olfactory dysfunction.[1–3] It is possible that IOD may represent an early manifestation of neurodegenerative disease in a select group of patients. For instance, Haehner et al[4] found that 10% of patients who were diagnosed with IOD ultimately developed Parkinson's disease after an 11-year interval. Thus, in some instances, the designation of IOD may be a misclassification, and current estimations of IOD prevalence may be artificially inflated. In cases of true IOD, a small body of literature utilizing neurophysiologic and neuroimaging techniques has attempted to elucidate the pathophysiology with limited success.

Perturbations in the central nervous system and olfactory pathways are potentially implicated in the pathogenesis of IOD. Several studies have shown that olfactory performance correlates with cortical volume of the orbitofrontal cortex (OFC) and insular cortex (IC) in healthy adults.[5,6] Moreover, these portions of the brain decline in volume in patients with

diverse etiologies of olfactory dysfunction.[7] Yao et al[8] showed that in a population of IOD patients, significant grey matter volume decline was seen in the primary olfactory cortex (PC), and secondary olfactory areas (OFC, IC, anterior cingulate cortex (ACC), parahippocampal cortex (PPA). Olfactory bulb volume changes are common in many etiologies of olfactory dysfunction, including patients with IOD, and are thought to represent a declining population of olfactory neurons secondary to decreased olfactory signal transduction from the neuroepithelium.[9–11] Despite the concordance of these findings in patients with IOD, there are conflicting reports that fail to demonstrate identifiable radiologic irregularities.[3] Moreover, it is unknown if structural changes in the brain are a consequence of the pathophysiologic mechanism of IOD, or rather, a secondary manifestation of diminished olfactory function.

Beyond radiologic findings, patients with IOD may have alteration in olfactory signal transduction. Liu et al[11] compared the amplitude and latency of chemosensory event-related potentials in patients with IOD and normal healthy controls. In patients with IOD, a significant decrease in amplitude of event-related potentials likely represented either decreased populations of peripheral olfactory neurons or alterations in central olfactory pathways.

The current body of literature implicates central nervous system structural changes and electrophysiologic signal transduction dampening in the pathophysiologic mechanism of disease. Significant work remains to fully elucidate this disease process, which may, in fact, reflect multiple underlying etiologies.

Table VII.18 Section Evidence Summary Table: Idiopathic

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Rombaux et al[10]	2010	4	Case control study	1) Idiopathic olfactory loss 2) Matched controls	1) Psychophysical olfactory testing (Sniffin' Sticks) 2) MRI brain findings	1) Olfactory bulb volume smaller in patients with idiopathic loss as compared to controls 2) Olfactory bulb volume correlates with threshold scores

Fonteyn et al[1]	2014	4	Case series	Heterogenous population with diverse olfactory loss etiology	1) Orthonasal psychophysical olfactory testing (Sniffin' Sticks) 2) Retronasal psychophysical olfatory testing (powder application)	1) IOD represented 16.3% of diverse olfactory loss population 2) Orthonasal and retronasal testing scores were statistically correlated in IOD patients
Hoekman et al[3]	2014	4	Case series	Patients with idiopathic olfactory loss	MRI brain findings	Less than 1% of included patients with attributable radiologic lesion
Yao et al[8]	2014	4	Case control study	1) Idiopathic olfactory loss 2) Matched controls	1) Psychophysical olfactory testing (Sniffin' Sticks) 2) MRI brain findings	Decreased gray matter volume in primary and secondary olfactory centers of the brain in patients with idiopathic loss compared to controls
Hald et al[2]	2020	4	Case series	1) Idiopathic olfactory dysfunction 2) Sinonasal OD 3) Post-infectious OD	1) Psychophysical olfactory testing (Sniffin' Sticks) 2) Gustatory testing (taste drop and spray tests) 3) Neurologic and Psychiatric Screening (MMSE, MDI)	1) No difference in neurologic and psychiatric screening between groups 2) IOD represented 30% of patient population
Liu et al[11]	2018	4	Case control study	1) Idiopathic olfactory dysfunction 2) Matched controls	1) Psychophysical olfactory testing (Sniffin' Sticks and T&T olfactometer) 2) Electrophysiologic testing (EEG, ERP) 3) MRI brain findings	1) Decreased amplitude of olfactory ERP in patients with IOD compared to controls 2) Olfactory bulb volume smaller in patients with idiopathic loss compared to controls

Abbreviations: EEG, electroencephalogram; ERP, event-related potentials; MMSE, mini-mental state examination; MDI, major depression inventory; TDI, threshold/discrimination/identification.

- **A significant portion of olfactory loss patients are placed into an idiopathic category, with likely multiple different etiologies leading to this diagnosis. More research is needed to better elucidate and therefore treat the underlying mechanisms.**
  Aggregate grade of evidence: C (Level 4: 6 studies)

SECTION: VIII. Evaluation and Diagnosis

A. History and Physical Exam

History and physical examination are essential parts of the evaluation of patients with olfactory dysfunction.[1–9] A thorough history provides a diagnosis of olfactory dysfunction in most cases and a complete head and neck examination helps to confirm the diagnosis. Multiple retrospective case series and a prospective cohort study have used clinical history and physical examination to delineate potential etiologies among patients presenting with olfactory dysfunction (**Table VIII-1**).[1–5,8,9] There were no randomized studies investigating the utility of the history-taking or physical exam on the diagnosis of olfactory dysfunction. Lack of higher-level evidence is expected given that history and physical exams are essential to any medical diagnosis.

Clinical assessment of patients with olfactory dysfunction should include general clinical history and specific questions related to olfactory disorders. Several guidelines and multiple expert opinions suggest clinical history to include the quality of olfactory changes, timing of onset, duration, associated factors, and social and family history.[6,7,10,11] History of olfactory dysfunction requires clarification on the quality of dysfunction (anosmia, hyposmia, dysosmia, parosmia, or phantosmia; definitions described in **section III: A–D**), laterality (unilateral or bilateral), perceived degree of smell loss (partial or complete), and olfactory status prior to loss. Information on timing of onset and duration includes whether the patient ever had olfaction (congenital or acquired), sudden or gradual onset, and whether the symptoms are persistent or intermittent. Patients may present with concurrent gustatory dysfunction.[1,5] Patients with olfactory dysfunction frequently confuse symptoms of flavor loss resulting from the smell

disturbance, with true taste dysfunction.[1] Further clarification on whether patients have primary gustatory dysfunction or taste alteration due to an olfactory disorder with the preservation of basic taste perceptions (sweet, bitter, sour, and salt) is important.

Factors associated with potential causes of the olfactory dysfunction can be obtained from history. Notably, clinicians should obtain detailed history on sinonasal symptoms and infectious or traumatic events preceding the onset of olfactory dysfunction as sinonasal diseases, post-infectious and post-traumatic olfactory disorders represent more than two-thirds of patients presenting with olfactory dysfunction. Related sinonasal factors include previous upper respiratory infection (URI), sinusitis, allergy, nasal obstruction and epistaxis.[12,13] Olfactory dysfunction during an acute URI or sinusitis can initially represent a conductive loss, but persistent dysfunction after resolution of infectious symptoms may indicate sensorineural injury to the olfactory epithelium.[2,5] History of previous head trauma, nose/sinus surgeries, head and neck cancer and radiation is important in determining the etiology of olfactory dysfunction.[14,15] Loss of smell related to trauma more commonly presents with sudden onset and complete anosmia in comparison to URI-related dysfunction more commonly resulting in hyposmia.[1,2,5,16] The nature and severity of the traumatic injury and the time course can be obtained. History of previous septum or sinus surgery should be asked as associated partial and complete smell loss has been reported.[17,18]

Social history includes history of occupational and environmental exposure to toxins and substance use (i.e. alcohol, smoking, cocaine, and other inhalants).[19,20] Clinicians should ask about exposure to toxins previously known to cause loss of smell including various metals (cadmium, chromium, manganese, mercury, aluminum, and lead), gases (formaldehyde, methyl bromide, and styrene), and solvents (toluene and paint solvents).[1] Tobacco smoking history along with other substance use should be obtained in assessment of olfactory dysfunction.[19]

Other symptoms in relation to mental status changes, cognitive dysfunction, and psychiatric complaints associated with depression, schizophrenia, and bipolar disorders can be obtained from history.[21–24] About 50-90% of patients diagnosed with Alzheimer's or Parkinson's diseases are affected by smell loss.[21,23–26] Olfactory dysfunction has been identified as one of the early manifestations of the neurodegenerative diseases more commonly presenting with

gradual onset hyposmia without obstructive symptoms.[27–29] Family history of neurodegenerative diseases and complete medication list need to be additionally reviewed.

Physical examination includes a full head and neck examination followed by nasal endoscopy, otoscopy, and neurological exam including cranial nerve exam.[1–6,8] Initial anterior rhinoscopy with a nasal speculum can help in assessing anterior deformities including obvious septal deviation and turbinate enlargement. Nasal endoscopy (rigid or flexible) allows for more thorough evaluation of the entire sinonasal area including posterior nasal cavity and nasopharynx. During nasal endoscopy, olfactory cleft and middle meatus should be carefully evaluated to rule out obstructive etiologies.[6,30] Validated clinical scoring systems such as the Lund-Kennedy scoring system[31] or the Olfactory Cleft Endoscopy Scale[32] can be used to document the nasal endoscopy findings. Nasal endoscopy has been shown to be more sensitive than anterior rhinoscopy in detecting nasal obstructive diseases. Seiden et al[8] found that olfactory dysfunction with obstructive etiology was successfully diagnosed in 91% of cases with nasal endoscopy in comparison to 49% with anterior rhinoscopy. Use of intranasal anesthesia prior to nasal endoscopy may affect chemosensory test results and the clinical history itself. Welge-Lussen et al[9] demonstrated that application of the intranasal anesthesia reduces self-assessment of olfaction and odor discrimination among healthy volunteers.[9] Therefore chemosensory testing and obtaining the complete history should be done prior to application of topical anesthetic. Otoscopy can be used to rule out obvious middle ear pathology that can affect the chorda tympani nerve and its associated taste impairment.[33] For cases related to traumatic injury in acute settings, close inspection of laceration, ecchymosis, and edema is advised to assess potential skull base and facial fractures that are associated with shearing or stretching injury of the olfactory nerves at the cribriform plate.[34] Basic neurological and mental status exam can be considered if dementia or other neurodegenerative disorders are suspected.[6] Appropriate referral to specialists should be considered if either neurologic or neurotologic causes are suspected.

Table VIII.1. Section Evidence Summary Table: History and Physical Exam to guide Diagnosis

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Deems[1]	1991	4	Case series	Subjective olfactory or gustatory dysfunction (n=750)	History, physical exam, chemosensory test	History and physical exam were used to delineate potential etiologies of olfactory dysfunction.
Temmel et al[2]	2002	4	Case series	Objective hyposmia or anosmia (n=278)	History, physical exam, chemosensory test	History and physical exam were used to delineate potential etiologies of olfactory dysfunction.
Landis et al[3]	2004	4	Prospective cohort study	All patients seen in a tertiary center clinic (n=1240)	History, physical exam, chemosensory test	History and physical exam were used to delineate potential etiologies of olfactory dysfunction.
Frasnelli et al[4]	2004	4	Case report	Selected cases of olfactory	History, physical exam, chemosensory test	Olfactory dysfunction presented in

				dysfunction (n=5)		various qualities and associated symptoms.
Harris et al[5]	2006	4	Case series	Subjective olfactory or gustatory dysfunction (n=1,000)	History, physical exam, and chemosensory test	History and physical exam were used to delineate potential etiologies of olfactory dysfunction.
Hummel et al[6]	2017	5	Guideline	n/a	Recommendations on diagnosis and management of olfactory dysfunction	History and full head and neck exam with endoscopy are recommended for patients with suspected olfactory loss. Basic neurological exam is recommended for patients with potential underlying neurological etiology although formal neurocognitive

						testing can be deferred to the specialist.
Miwa et al[7]	2019	5	Guideline	n/a	Recommendations on management of olfactory dysfunction	Various management options are available for patients presenting with olfactory dysfunction by etiology.
Seiden and Duncan[8]	2001	4	Case series	Subjective olfactory dysfunction (n=428)	History, physical exam, chemosensory test	History and physical exam were used to delineate potential etiologies of olfactory dysfunction. Anterior rhinoscopy failed to diagnose conductive pathology in 51% of cases in comparison to 9% with nasal endoscopy.

Welge-Lussen et al[9]	2004	3b	Non-randomized experimental trial	Healthy volunteers (n=20)	Nasal endoscopy, chemosensory test	Intranasal anesthesia reduced self-assessment of olfaction independent of the application location. Intranasal anesthesia applied in the middle nasal meatus elevated olfactory threshold and lowered odor discrimination.

A complete history and physical exam, including nasal endoscopy, allows for appropriate diagnosis and management of olfactory dysfunction.
Aggregate Grade of Evidence: C (Level 4: 6 studies; Level 5: 2 studies)
Benefit: Complete history and physical exam, with nasal endoscopy, guides the choice of appropriate diagnostic tests, helps avoid misdiagnosis, improves diagnostic accuracy, ensures that treatment is consistent with diagnosis, guides patient expectations
Harm: Minimal discomfort during physical exam and nasal endoscopy
Cost: Minimal, although cost of a doctor's visit is dependent on health care system
Benefits-Harm Assessment: Preponderance of benefit over harm
Value Judgments: none
Policy Level: Strong recommendation
Intervention: History taking and basic physical exam are essential in the diagnosis of olfactory dysfunction. Nasal endoscopy is additionally recommended to make an accurate diagnosis, as when it is combined with patient history, it increases diagnostic accuracy and excludes alternative causes.

SECTION: VIII. Evaluation and Diagnosis

B. Imaging

Classic work-up of patients with olfactory dysfunction (OD) relies on thorough medical history, clinical examination and evaluation of olfactory function. This work-up allows for diagnosing OD and its etiology in many patients. Additionally, imaging procedures are useful to better define the cause of OD, to rule out central nervous system disease processes including tumors, as well as to counsel patients regarding overall prognosis.

In this review, we have analyzed evidence for the use of diverse imaging modalities in patients with OD.

1. Computed tomography (CT) of the paranasal sinuses

There are 4 studies evaluating the usefulness of CT of the paranasal sinuses in patients with OD (**TableVIII.2**). All of these studies use non-contrast CT, viewed on bone window.

Three studies (2 case series and 1 prospective cohort study) found that CT was useful in identifying olfactory cleft obstruction, in the context of obstructive OD,[1] COVID-19 related OD,[2] and olfactory cleft syndrome.[3] One retrospective study evaluated the usefulness of CT-scan to diagnose OD resulting from sinonasal disease (SND), in comparison to clinical examination.[4] This study found that CT could be useful in refining the diagnosis since it was able to both diagnose SND in 7% of patients suspected of non-SND etiologies, as well as rule out SND in one third of patients with suspected SND, who then had normal CT imaging. Specifically, they found that 3% of patients with post-infectious, 14% with post-traumatic, and 11% of patients with idiopathic olfactory dysfunction had signs of sinonasal inflammation. The authors therefore propose that CT scans are useful in patients suspected of non-SND olfactory dysfunction to diagnose a possible contributory component of inflammatory olfactory loss. Indeed, identifying a conductive or an inflammatory cause underlying an olfactory disorder is particularly important since these patients could benefit from known medical/surgical interventions directed at SND, possibly improving olfactory function. Although CT imaging could bring valuable information, it has to be emphasized that conductive or inflammatory causes can also be identified, in a majority of

patients, based on careful medical history taking and endoscopic examination. In these cases, adequate treatment will be proposed prior to CT imaging, according to available guidelines.[5] CT scan (or other imaging, such as MRI) should be considered if the patient has unilateral pathology, suspicion of tumor, or after failure of appropriate medical treatment. If tumor or malignancy is suspected, medical and imaging work-up should be completed expeditiously.

Table VIII.2. Sinus computed tomography (CT)

Study	Year	LOE	Study design	Study groups	Clinical End-Point	Conclusion
Yildirim et al[1]	2020	3	Prospective cohort study	106 patients with olfactory dysfunction (OD) (41 post-infectious (PI), 13 post-traumatic (PT), 28 idiopathic and 17 obstructive); 17 normosmic controls	- Anterior cranial fossa fractures (CT) - Aeration of the olfactory cleft (CT) - Olfactory function (Sniffin' Sticks Test (SST)) - MRI of olfactory pathways (see table 2)	Obstructive group was characterized by loss of aeration of the olfactory cleft
Kandemirli et al[2]	2020	4	Prospective case series	23 patients with persistent COVID-19 related OD	- Olfactory function (SST) - Olfactory cleft aeration pattern (CT) - MRI of olfactory	Olfactory cleft opacification was seen in 73.9% of cases

					pathways (see table 2)	
Mueller et al[4]	2006	4	Retrospective study	137 patients with OD	- Olfactory function - CT-scan of the paranasal sinuses - Assumed diagnosis (sinonasal disease (SND) related or not) vs. CT-based diagnosis	CT diagnosed SND in 7% patients suspected of non-SND; one third of patients with suspected SND prior to imaging had normal CT.
Biacabe et al[3]	2004	4	Retrospective case series	13 patients with olfactory cleft disease	- Olfactory threshold test - Endoscopic evaluation - CT scan of the paranasal sinuses	CT scan provided useful information for diagnosing OCS

CT Imaging for Evaluation and Diagnosis of Olfactory Dysfunction

Aggregate grade of evidence: D (Level 3: 1 study, Level 4: 3 studies)
Benefit: potential identification of treatable obstruction of the olfactory cleft or sinonasal disease
Harm: minimal (low radiation dose using cone-beam CT)
Cost: moderate
Benefit-Harm assessment: relative balance of benefit and harm given low risk of imaging and yet low level of evidence
Value judgments: The question as to whether CT scan brings relevant additional information that will change the management and outcome of patients with normal endoscopic examination, or with OD due to clearly attributable cause (post-infectious or post-traumatic) remains unanswered and no recommendation can be made. In post-traumatic OD, CT scan can be considered for identifying bony sequalae (septal fracture, fracture to the cribriform plate) or

when a CSF leak is suspected. When olfactory dysfunction is suspected to be from sinonasal inflammatory causes, a CT is helpful in confirming that.
Policy level: Option
Intervention: In case of suspected olfactory cleft syndrome or sinonasal disease causing olfactory dysfunction, CT scan can be considered as an option to confirm the diagnosis. There is low level evidence to support its use in other causes of olfactory dysfunction.

2. **Structural MRI**

Thirty-two studies assessing the morphology of olfactory pathways in patients with OD using structural MRI met our inclusion criteria (**Table VIII.3:** 12 prospective cohort studies; 8 case series; 12 retrospective studies).

As a major relay of the olfactory pathways, the most studied structure is the olfactory bulb (OB), which can be easily visualized on MRI without contrast. Indeed, a large number of studies have evaluated its morphology, and particularly its volume. The majority of studies (9 prospective cohort studies, 6 case series and 6 retrospective studies) agree that OB volume is decreased in patients suffering from a wide range of pathologies affecting olfactory function.[1,2,6,7,9–11,13,15,16,19,22,25,28–35] Indeed, patients with post-traumatic,[15,21,32] post-infectious,[7,15] idiopathic,[1,6,11] obstructive,[1] and congenital.[16,25] OD were found to have smaller OB compared to normosmic controls.

Several studies (2 prospective cohort studies, 3 case series and 4 retrospective studies) have also found a positive correlation between OB volume and olfactory function,[11,15,23,27–30,34] notably in post-infectious,[15,28,30] post-traumatic,[15,29,32,34] and idiopathic[11] OD. However, some studies (1 prospective cohort study, 1 case series) found no correlation between OB volume and olfactory function.[13,18] In the same vein, it has been described (1 prospective cohort study, 1 retrospective study) that OB volume correlates to the results of olfactory event-related potentials.[13,22] Qualitative OD also seems to be associated with OB reduction, since three studies (1 prospective cohort study, 2 retrospective studies) have found that patients with parosmia have smaller OB volume.[15,29,30]

Structural MRI studies have also investigated the plasticity of the OB over time. One prospective cohort study found that OB volume is inversely correlated to the duration of the

olfactory loss.[7] Another prospective cohort study showed that changes in olfactory function over time is correlated to change in olfactory bulb volume.[14]

Three studies (1 case series, 2 retrospective studies) have assessed the prognostic value of the OB. Some authors have found that the OB volume and integrity are prognostic factors of recovery in post-infectious[27] and post-traumatic[17,27] olfactory loss. In contrast, others found that the OB volume was not an indicator of the prognosis of recovery[20] in patients with idiopathic OD.

Another anatomical structure that has been widely investigated is the olfactory sulcus (OS). OS depth was reported (3 prospective cohort studies, 1 retrospective study) to be smaller in patients with OD from various origins (post-infectious,[1] post-traumatic,[1] idiopathic,[1] congenital[9,10,16,25]), while other studies found no difference in idiopathic OD[6,11] (2 prospective cohort studies) or posttraumatic OD[18] (1 case series). It was also reported in one retrospective study that OS depth was correlated with olfactory function in patients with all causes of OD.[23]

It also appears from MRI studies that some etiologies have characteristic imaging features, rendering MRI useful to confirm the etiology of OD. Indeed, it was reliably found that patients with congenital anosmia have severely hypoplastic or aplastic OB, and a shallow olfactory sulcus.[9,10,16,25,31,35] In post-infectious olfactory loss, OB volume is decreased, and the OB may exhibit signal changes with central hyper-T2 signal[2]. Patients with post-traumatic olfactory dysfunction exhibit typical lesions, mainly at the level of the OB, OT, temporal and/or frontal lobes.[8,12,21,32–34] MRI has been found to have a high accuracy in detecting post-traumatic OD[26]. The earliest study about MRI in post-traumatic OD reported that 88% of patients had abnormal MRI findings.[34] Therefore, MRI is of paramount importance for the medico-legal assessment of post-traumatic OD.

MRI is also interesting to evaluate the global brain morphology and olfactory pathways. Besides showing typical lesions in patients with post-traumatic olfactory loss, it has been described that olfactory function was associated with overall MRI brain changes[18] (1 case series) but also that parosmia and phantosmia could be related to lesions in specific brain areas[21] (1 retrospective study). In addition, brain MRI is also considered to reveal potential intracranial causes underlying idiopathic OD, and notably, to exclude brain tumors. A retrospective study[24] evaluated the cost-effectiveness of MRI in patients with idiopathic OD and

found that abnormalities were identified in 4.6% of patients, with only 0.8% of patients having OD attributable to an imaging finding. The investigators estimated that the cost per attributable abnormal finding was 325,000 USD. Therefore, the routine use of MRI in patients with idiopathic OD is debatable.

It is widely acknowledged that olfactory loss may constitute an early sign of neurodegenerative diseases (ND), such as Parkinson's or Alzheimer's diseases. Therefore, patients with idiopathic smell loss are at times considered as at-risk to develop ND. However, no study has investigated the usefulness of structural MRI for the early diagnosis of these diseases in patients with idiopathic smell loss.

Table VIII.3. MRI

Study	Year	LOE	Study design	Study groups	Clinical End-Point	Conclusion
Yildirim et al[1]	2020	3	Prospective cohort study	106 patients with olfactory dysfunction (OD) (41 post-infectious (PI), 13 post-traumatic (PT), 28 idiopathic and 17 obstructive); 17 normosmic controls	- Morphology of the olfactory bulb (OB) and olfactory nerve - OB volume - Olfactory function (SST) - CT of the anterior cranial fossa and olfactory cleft (see Table 1)	OB volume was decreased in idiopathic and obstructive groups compared to controls; OS was smaller in all groups of OD; OB had morphological particularities in PI and idiopathic; fronto-basal lesions were present in PT
Liu et al[6]	2018	3	Prospective cohort study	20 idiopathic OD, 20	- Olfactory function (Toyota and Takagi scores (T&T))	Patients with idiopathic OD had significantly

				normosmic controls	- Chemosensory event-related potentials - OB volume and OS depth	smaller OB volumes. No difference was found in OS depth
Yao et al[7]	2018	3	Prospective cohort study	19 PI OD, 19 normosmic controls	- Olfactory function (T&T) - OB volume - Voxel-based morphometry (see table 3) - Time since injury	PI OD was associated to decreased OB volume; duration of olfactory loss was negatively correlated with OB volume
Lötsch et al[8]	2015	3	Prospective cohort study	41 patients with PT OD 23 patients with non-PT OD	- Olfactory function (SST) - Damages in 11 olfactory-relevant brain areas - Development of an olfactory diagnostic algorithm	Lesions in OB, OT and temporal lobe pole were able to predict PT anosmia with a high accuracy
Ottaviano et al[9]	2015	3	Prospective cohort study	38 patients with Kallmann syndrome (KS); 21 normosmic controls	- Olfactory function (SST) - OB, OT and OS morphology	KS patients had significantly reduced OB volume and OS depth; thicker cortex in region close to OS; olfactory function correlated with OB volume and cortical thickness
Huart et al[10]	2012	3	Prospective cohort study	36 patients with CA, 70	- Depth of the OS	Patients with CA had smaller OS

				normosmic controls		depth; OS ≤ 8mm clearly indicated CA with a specificity of 1
Rombaux et al[11]	2010	3	Prospective cohort study	22 patients with idiopathic OD; 22 normosmic controls	- Olfactory function (SST) - OB volume and OS depth	OB volume was smaller in idiopathic OD; OS depth showed no difference; odor thresholds correlated with OB volume
Altighechi et al[12]	2009	3	Prospective cohort study	21 patients with PT OD; 19 PT patients without OD; 63 normosmic healthy controls	- Olfactory function (Cain's identification test) - MRI: OB morphology, brain lesions - SPECT: brain perfusion (see Table 4)	PT anosmics exhibited damage to frontal lobes and OB
Goektas et al[13]	2009	3	Prospective cohort study	10 patients with PI OD; 5 patients with PT OD; 9 patients with idiopathic OD	- Olfactory function (SST) - Chemosensory ERPs - OB volume	Association between OB volume and presence of olfactory ERPs; no correlation between OB volume and TDI score
Haehner et al[14]	2008	3	Prospective before-after trial	20 patients with olfactory loss	- Olfactory function (SST) at baseline and follow-up	OB volume changes correlated with odor threshold changes

					- OB volume at baseline and follow-up	
Mueller et al[15]	2005	3	Prospective cohort study	22 patients with PI OD; 9 patients with PT OD; 17 normosmic controls	- Olfactory function (SST) - OB volume	OB were smaller in patients with OD compared to controls; OB volume correlated with olfactory function; OB were smaller in patients with parosmia
Abolmaali et al[16]	2002	3	Prospective cohort study	16 patients with CA; 8 normosmic controls	- Assessment of fronto-basal structures	CA patients had aplastic or hypoplastic OB; OS depth reflected the presence of OT
Kandemirli et al[2]	2020	4	Case series	23 patients with persistent COVID-19 related OD	- Olfactory function (SST) - OB volume and quality and OS depth - CT of the olfactory cleft (see table 1)	OB abnormalities were seen (hypoplastic – 43%, signal abnormalities – 91.3%); primary olfactory cortex showed signal abnormalities in 21% cases
AbdelBari et al[17]	2020	4	Retrospective	70 patients with PT olfactory dysfunction	- OB integrity - Olfactory function (SST)	OB integrity was a prognosis factor for olfactory recovery
Langdon et al[18]	2018	4*	Prospective randomized controlled	42 patients with PTOL	- Olfactory function (VAS, BAST-24, n-butanol thresholds)	Olfactory function was significantly associated with the overall MRI

					- MRI traumatic lesion score	score, but not with the olfactory bulb (OB) volume or olfactory sulcus (OS) length
Chung et al[19]	2018	4	Retrospective case series	34 patients with OD	- Olfactory function (Korean version of the SST) - Questionnaires (SNOT-22, QOD) - OB volume and signal	OB atrophy was significantly higher in patients with anosmia/hyposmia vs. normosmia. No difference in OB signal between groups
Shiga et al[20]	2017	4	Retrospective case series	24 patients with idiopathic OD	- Olfactory function (T&T) at baseline and after treatment with Japanese herbal medicine - OB volume at baseline - Olfacto-scintigraphy (nasal thallium administration and SPECT-CT) at baseline (see Table 4) - Prognosis of recovery	OB volume was not an indicator of the prognosis of recovery
Lötsch et al[21]	2016	4	Retrospective	143 patients with PT OD	- Olfactory function (SST) - Brain lesions pattern analysis	Higher prevalence of parosmia and tendency to phantosmia in subjects with

						medium overall brain damage; lower frequency of lesions in the right temporal lobe in parosmia; lesions of the right olfactory bulb were more frequent in anosmia; higher frequency of left frontal lobe lesions in phantosmia
Miao et al[22]	2015	4	Retrospective cohort study	26 patients with PT OD; 21 normosmic controls	- Olfactory function (T&T) - Chemosensory event-related potentials (ERPs) - OB volume, OS depth, brain lesions	OB volume was decreased in PT OD. Lesions at the level of the OB, OT and gyrus rectus were associated to the results of the olfactory ERPs
Hummel et al[23]	2015	4	Retrospective case series	378 patients with OD	- Olfactory function (SST) - OB volume, OS depth	Correlation between OB volume and olfactory function; right OS correlated with olfactory function; OS was negatively correlated with age
Hoekman et al[24]	2014	4	Retrospective case series	247 patients with	- Olfactory function (UPSIT)	Abnormalities were identified in

				idiopathic OD (130 were scanned using MRI)	- MRI findings - Cost-effectiveness	4.6%; 0.8% of patients had olfactory loss attributable to imaging findings; the estimated cost per attributable abnormal finding was $325,000
Levy et al[25]	2013	4	Retrospective cohort study	40 patients with isolated CA; 22 normosmic controls	- Olfactory function (detection and recognition) - OB, OS olfactory groove and hippocampal morphology	Patient with CA may show aplastic or hypoplastic OB, decreased OS depths and/or abnormalities in hippocampal anatomy
Atighechi et al[26]	2013	4	Retrospective case series	63 patients with PT OD	- Olfactory function (Cain's smell test) - MRI: abnormalities of the OB, OT, frontal and temporal lobes - SPECT: perfusion in the frontal and temporal lobes (see Table 4)	MRI and SPECT had high sensitivity and specificity in the diagnosis of PT anosmia, with SPECT having better performances than MRI
Rombaux et al[27]	2012	4	Prospective case series	60 patients with OD (28 PI; 32PT)	- Olfactory function (SST) (baseline and follow-up) - MRI: OB volume - Recovery	OB volume correlated with olfactory function at baseline and with the improvement of olfactory function at follow-up

Rombaux et al[28]	2009	4	Retrospective case series	122 patients with PI OD	- Olfactory function (SST, retronasal) - Chemosensory ERPs - OB volume	OB volume correlated to psychophysical (ortho- and retronasal) olfactory tests
Rombaux et al[29]	2006	4	Retrospective case series	25 patients with PT OD	- Olfactory function (SST, retronasal) - OB volume and brain damages	Olfactory function correlated with OB volume; retronasal function was more affected with more extensive cerebral lesions; parosmia was associated with smaller OB and the presence of cerebral damage
Rombaux et al[30]	2006	4	Retrospective case series	26 patients with PI OD	- Olfactory function (SST) - OB volume	OB volume was negatively correlated to olfactory function; was decreased with duration of olfactory loss; was smaller in patients with parosmia
Aiba et al[31]	2004	4	Prospective case series	9 patients with CA	- Olfactory pathway morphology	7 patients had abnormalities of OB, OT, OS or gyrus rectus
Yousem et al[32]	1999	4	Prospective case series	36 patients with PT OD; 24	- Olfactory function (UPSIT) - OB, OT, temporal lobes	PT lesions were mainly seen in OB, OT, subfrontal and temporal lobes;

				normosmic controls		OBT volume correlated with identification performances; PT patients had smaller OB volumes
Doty et al[33]	1997	4	Prospective case series	268 patients with PT OD (MRI was performed in 15)	- Olfactory function (UPSIT) - Morphology of olfactory related brain structures	MRI is able to identify damage in olfactory-related brain structures
Yousemet al[34]	1996	4	Prospective case series	25 patients with PT OD	- Olfactory function (UPSIT) - Morphology of olfactory-related brain structures	88% PT patients had abnormal MRI; lesions mainly involved OB, OT and inferior frontal lobes; more severe OD was associated to greater OB and OT volume loss
Yousem et al[35]	1996	4	Prospective case series	25 patients with CA	- Olfactory function (UPSIT) - Morphology of olfactory-related brain structures	AC had aplastic or hypoplastic OB and OT
*Adjustment was made toward reduction of quality since randomization was made regarding olfactory training while imaging results were analyzed at the level of the whole group (similarly to a case series study).						

MR Imaging for Evaluation and Diagnosis of Olfactory Dysfunction

Aggregate evidence: C (Level 3: 12 studies, Level 4: 20 studies)
Benefit: Identification/confirmation of the etiology, exclusion of intracranial tumor, objective correlate of olfactory function and prognosis, medico-legal value
Harm: Minimal

Cost: High
Benefit-Harm assessment: Relative balance of benefit and harm
Value judgments: While MRI has been found to be very useful in some cases, only low level evidence supports its use and it is costly.
Policy level: Option
Intervention : MRI is considered as the gold-standard imaging procedure for the evaluation of patients with OD from non-sinonasal inflammatory causes, and may be considered as an option. The use of MRI is potentially valuable in patients with congenital and post-traumatic anosmia. It can be considered in patients with idiopathic OD to exclude intracranial pathology. Its use in post-infectious OD is debatable considering its low added value to clinical history with regard to management of patients. It should be further investigated whether the use of MRI changes the management and outcome of a select group of these patients, and consequently define which patients with OD would benefit most from MRI.

3. Advanced MRI techniques (requiring research facility/environment)

Advanced morphological or functional MRI techniques have also been used to investigate olfactory-brain related morphology and function (**Table VIII.4:** 18 prospective cohort studies, 1 case series). These techniques are usually not feasible or useful in clinical routine and require a specific research environment and the use of specific devices and software.

We found 7 functional MRI (fMRI) studies (6 prospective cohort studies, 1 case series) related to olfactory function. These studies found that brain activation is related to olfactory function, with decreased activation of primary and secondary olfactory cortices following olfactory stimulation in patients with post traumatic anosmia.[36,37] Moreover, brain activation was found to be negatively correlated to the duration of the disease,[37] and recruitment of neural network was associated with olfactory function.[38] In contrast, a study specifically assessing hyposmic patients showed similar central olfactory processing compared to controls. However, hyposmics had higher activation in regions associated to odor memory and motivation, possibly as a result of compensation.[39] In patients with longterm OD, fMRI demonstrated changes in functional connectivity after 12 weeks of olfactory training (OT), albeit in a series including only a very small number of patients.[40] Recently, one study aimed to evaluate the clinical usefulness of fMRI for the evaluation of patients with OD. It has shown that BOLD signal is not able to discriminate between patients with OD and controls, due to large inter-individual variability. Moreover, there was no correlation between olfactory function and fMRI parameters.[41]

Studies using resting-state fMRI to study functional connectivity found either no difference in functional connectivity in the olfactory network in patients with congenital anosmia[42] or changes in olfactory and global brain network connectivity in patients with post-traumatic OD.[43]

We found 10 prospective cohort studies based on advanced morphological MRI. Among these studies, 9 evaluated patients based on voxel-based morphometry. Assessing patients with congenital anosmia, one study found that congenital anosmia was associated with morphological alterations at the level of the secondary olfactory cortex, but not to the primary olfactory cortex[44]; another found that congenital anosmics have larger gray matter volume in both primary and secondary olfactory cortices.[45] In patients with post-infectious olfactory loss, it has been reported that there is a gray matter volume loss in diverse brain-related olfactory areas (notably in the orbito-frontal cortex)[46,47] and that olfactory training is associated with a regain in the volume of affected regions.[46] Patients with idiopathic OD were also found to exhibit gray matter volume loss in primary and secondary olfactory areas.[47] Based on olfactory function, patients with anosmia and hyposmia exhibited decreased gray and white matter volume[48–50] and it has been found that patients with parosmia have a gray matter volume loss in regions associated with olfactory discrimination and memory.[51] Moreover, it has been described that disease duration influenced brain atrophy since atrophy increased with duration[12,48] in patients with post-infectious and idiopathic OD. Finally, using a deep learning model, a prospective cohort study suggested that MRI could be useful for the differential diagnosis between Parkinson's related OD and non-Parkinson's OD.[52]

Diffusion MRI has been investigated in two prospective cohort studies.[53,54] One study investigated patients with congenital anosmia and found that these patients have network dysfunction but intact structural integrity.[53] Another study investigated patients with idiopathic olfactory loss, considered as at risk to develop Parkinson's disease (PD), in comparison to PD patients and normosmic controls.[54] This study found that, on a group level, fractional anisotropy (FA) measured at the level of the substantia nigra (SN) was decreased in idiopathic and PD patients in comparison to controls. This finding suggested a reduced integrity of the SN in idiopathic smell loss patients, supporting their PD at-risk status. However, there is no follow-up

of these patients and whether they developed PD. Moreover, the authors mention that their analysis was not satisfactory when performed on an individual level.

Table VIII.4. Advanced MRI techniques (requiring research environment)						
Study	**Year**	**LOE**	**Study design**	**Study groups**	**Clinical End-Point**	**Conclusion**
Yunpeng et al[41]	2020	3	Prospective cohort study	22 subjects with OD (14 congenital, 8 idiopathic); 16 normosmic controls	- Olfactory function (SST) - fMRI: Brain activation following odorous stimulation	BOLD signal was not able to discriminate between patients with OD and controls due to large interindividual variabilities; no correlation between olfactory function and fMRI parameters
Tremblay et al[52]	2020	3	Prospective cohort study	15 patients with Parkinson's diseases; 15 patients with PI or sinonasal OD; 15 controls	- Olfactory function (SST) - MRI: OB volume and convolutional neural network analysis	Possible to discriminate between Parkinson related OD and non-Parkinson OD with an accuracy of 88.3%
Peter et al[44]	2020	3	Prospective cohort study	33 patients with congenital anosmia (CA),	- Olfactory function (SST) - Voxel-based morphometry	Morphological alterations were found in CA at the level of orbito-frontal

				34 normosmic controls	- Cortical thickness - OS depth	cortex (OFC); no morphological difference at the level of the primary olfactory cortex.
Peter et al[42]	2020	3	Prospective cohort study	33 patients with CA, 33 normosmic controls	- Olfactory function (SST) - Resting-state fMRI: functional connectivity	No difference in functional connectivity in the olfactory cortex
Chen et al[53]	2020	3	Prospective cohort study	20 patients with CA; 16 normosmic controls	- Olfactory function (SST and retronasal test) - DTI: Diffusion-tensor-based network analysis; fractional anisotropy (FA) measure	CA patients had network dysfunction but structural integrity (FA) remained intact; retronasal deficits were more associated with white matter (WM) alterations
Park et al[43]	2019	3	Prospective cohort study	16 patients with PT anosmia; 12 normosmic controls	- Olfactory function (Korean version of the SST) - Functional brain network connectivity (resting-state fMRI)	PT anosmia was associated with changes in olfactory and global brain network connectivity

Moon et al[36]	2018	3	Prospective cohort study	16 patients with PT anosmia, 19 normosmic controls	- Olfactory function (Korean version of the SST) - fMRI: Brain activation responses to olfactory stimulation	Brain activation was decreased in primary and secondary olfactory cortices in PT anosmia compared to controls
Yao et al[7]	2018	3	Prospective cohort study	19 patients with PI OD, 19 normosmic controls	- Olfactory function (T&T) - Voxel-based morphometry - OB volume (see table 2) - Time since injury	PI OD is associated to gray matter (GM) volume loss in right OFC; duration of olfactory loss is negatively correlated with OFC volume
Han et al[37]	2018	3	Prospective cohort study	40 patients with PT OD (19 hyposmia, 21 hyposmia); 19 normosmic controls	- Olfactory function (SST) - fMRI: brain activation to olfactory stimulation - Time since injury	PT OD had decreased odor-induced brain activation; brain activation was negatively correlated to time since injury
Gellrich et al[46]	2018	3	Cohort study	30 patients with PI OD; 31 normosmic controls	- Olfactory function (SST) (assessed before and after olfactory training in patients)	Before olfactory training, PI OD had decreased GM volumes in the limbic system and thalamus; after

					- Voxel-based morphometry	training these volumes were significantly increased
Haehner et al[54]	2018	3	Prospective cohort study	19 patients with idiopathic smell loss; 17 normosmic controls; 12 Parkinson disease (PD) patients	- Olfactory function (SST) - DTI, diffusion characteristics, FA measures	PD and idiopathic smell loss patients had significantly reduced FA values in the substantia nigra compared to healthy controls
Pellegrino et al[39]	2016	3	Prospective cohort study	11 hyposmic patients; 12 normosmic controls	- Olfactory function (SST) - fMRI: brain activation to olfactory stimulation	Hyposmics had similar central olfactory processing, but they had higher activation in regions associated to odor memory and motivation
Yao et al[47]	2014	3	Prospective cohort study	16 patients with idiopathic OD; 16 normosmic controls	- Olfactory function (T&T as SST) - Voxel-based morphometry	Idiopathic OD patients had reduced GM volume in primary and secondary olfactory areas
Peng et al[48]	2013	3	Prospective cohort study	19 anosmics; 20 normosmic controls	- Olfactory function (T&T) - Voxel-based morphometry	Patients with anosmia had a significant decrease in GM

						and corresponding WM volumes; atrophy increased with disease duration
Frasnelli et al[45]	2013	3	Prospective cohort study	17 patients with CA; 17 normosmic controls	- Voxel-based morphometry	CA had larger GM volumes in the left entorhinal and piriform cortices and thicker OFC bilaterally, and left piriform cortex.
Bitter et al[51]	2011	3	Prospective cohort study	22 patients with parosmia; 22 hyposmic controls without parosmia (matched for olfactory function)	- Voxel-based morphometry	Parosmia was associated with GM volume loss in regions associated with olfactory discrimination and memory
Bitter et al[49]	2010	3	Prospective cohort study	24 hyposmic patients; 43 normosmic controls	- Voxel-based morphometry	Hyposmic patients had GM and WM volume loss in several olfactory-related brain regions
Bitter et al[50]	2010	3	Prospective cohort study	14 anosmic patients; 17	- Voxel-based morphometry	Anosmic patients had significant

				normosmic controls		decrease of GM volume in several olfactory-related brain regions; longer disease duration was associated with increased atrophy
Reichert et al[38]	2018	4	Case series	48 patients with OD (29 anosmia, 19 hyposmia)	- Olfactory function (SST) - fMRI: brain activation to olfactory stimulation	The recruitment of neural networks was correlated to olfactory function
Kollndorfer et al[40]	2015	4	Case series	10 patients with OD, 14 healthy controls 7 with OD followed up after OT	- Olfactory function (SST) - fMRI: brain activation to olfactory stimulation	Neural networks utilized were the same between patients with OD and controls, but functional connectivity differed. Functional connectivity changed after 12 weeks of OT.

Use of Advanced MRI techniques for evaluation or management of OD

Aggregate evidence: C (Level 3: 18 studies, Level 4: 1 study)

Benefit: Clinical value at an individual level has not been demonstrated. Benefit in research realm only at this time.

Harm: Minimal

Cost: High

Benefit-Harm assessment: Balance of benefit and harm
Value judgments: These techniques require particular set-up, specific analytic techniques and expertise. Moreover, fMRI studies show a high inter-individual variability. Although these advanced techniques are useful for the understanding of olfactory processing, they are currently not adapted for use in the clinical setting.
Policy level: No recommendation for clinical purposes at this time.
Intervention : Currently, these techniques are not adapted to the clinical environment, and their value at an individual level is questionable. Research is needed to decrease the inter-individual variability and establish true clinical benefit before considering them for clinical use.

4. Nuclear medicine techniques

We have found six studies using nuclear medicine techniques to examine olfaction (**Table VIII.5**: 4 prospective cohort studies, 2 retrospective case series).

One prospective cohort study evaluated brain metabolism using FDG-PET under olfactory stimulation.[54] It showed that brain metabolism in certain brain regions is significantly different between patients with idiopathic OD and controls,[55] with a correlation between disease duration and FDG uptake.

Two studies (1 prospective cohort study and 1 retrospective case series) have investigated, using SPECT, the migration of nasally-administrated thallium. It was found that thallium migration to the OB was lower in patients with OD and correlated with olfactory threshold and with OB volume.[56] Also, high thallium migration was associated with a better prognosis of olfactory recovery.[20] Three other SPECT-based studies (2 prospective cohort studies and 1 retrospective case series) found that, after olfactory stimulation, the mean brain, frontal, temporal and parietal perfusions were significantly lower in patients with post traumatic OD.[12,57] Moreover, regional brain perfusion was able to diagnose post traumatic OD with a high accuracy,[26] that was even better than MRI.

Table VIII.5. Nuclear medicine techniques

Study	Year	LOE	Study design	Study groups	Clinical End-Point	Conclusion
Micarelli et al[55]	2017	3	Prospective cohort study	11 patients with idiopathic OD, 11	- Olfactory function (SST) - FDG-PET CT under	Brain metabolism was different in patients;

				normosmic controls	olfactory stimulation	negative correlation between disease duration and FDG uptake in left temporo-parietal joint
Shiga et al[56]	2013	3	Prospective cohort study	21 patients with OD; 10 normosmic controls	- Olfactory function (T&T) - Nasal thallium migration to the OB (SPECT-MRI) - MRI: OB volume	Thallium migration to the OB was lower in patients; was correlated with odor thresholds and with OB volume
Gerami et al[57]	2011	3	Prospective cohort study	20 patients with PT OD; 15 normosmic controls	- Olfactory function (UPSIT) - SPECT after olfactory stimulation	The mean brain perfusion was significantly lower in patients with PT OD
Atighechi et al[12]	2009	3	Prospective cohort study	21 patients with PT OD; 19 PT patients without OD; 63 normosmic healthy controls	- Olfactory function (Cain's identification test) - MRI: OB morphology, brain lesions (see Table 2) - SPECT: brain perfusion	PT anosmics have hypoperfusion in the frontal left parietal and left temporal lobes

Shiga et al[20]	2017	4	Retrospective case series	24 patients with idiopathic OD	- Olfactory function (T&T) at baseline and after treatment with Japanese herbal medicine - Olfacto-scintigraphy (nasal thallium administration and SPECT-CT) at baseline - OB volume at baseline (see table 2) - Prognosis of recovery	High Thallium migration to the OB is associated to better prognosis
Atighechi et al[26]	2013	4	Retrospective case series	63 patients with PT OD	- Olfactory function (Cain's smell test) - MRI: abnormalities of the OB, OT, frontal and temporal lobes (**see Table** 2) - SPECT: perfusion in the frontal	MRI and SPECT have high sensitivity and specificity in the diagnosis of PT anosmia, with SPECT having better performances than MRI

					and temporal lobes	

Use of Nuclear Medicine Imaging to Evaluate Olfactory Dysfunction
Aggregate evidence: C (Level 3: 4 studies, Level 4: 2 studies)
Benefit: SPECT could be beneficial for the diagnosis of post traumatic OD (e.g., medico-legal use). Nasal-Thallium migration could be indicative of the prognosis of recovery.
Harm: Minimal to moderate (use of radioisotopes)
Cost: High
Benefit-Harm assessment: Balance of benefit and harm
Value judgments: Nuclear medicine studies provide interesting results and seem promising. However, there are fewer studies, in comparison to MRI. Moreover, they require the use of radioisotopes, some of which are not routinely available. For a majority of clinical centers, the gold-standard MRI is probably more accessible and has less potential harm.
Policy level: **Option**
Intervention : Currently, MRI remains the gold-standard to evaluate patients with OD. Nuclear medicine techniques can be considered in particular cases or when MRI is not accessible or not feasible (contraindications to MRI).

SECTION: VIII. Evaluation and Diagnosis

C. Use of validated quantitative smell tests

It is well established that patients have difficulty assessing the degree of their own olfactory function. Self-ratings of smell function only rarely correlate well with quantitative measures of such function, with some patients believing they have severe loss when this is not the case and other patients being totally unaware of significant dysfunction until being tested.[1–11] Among variables that accentuate such discrepancies are older age and poorer cognition.[12] Clearly, reliable and valid tests are needed to accurately define a patient's function, establish efficacy of medical or surgical interventions, aid in differential diagnosis, and detect malingering. Unlike hearing, balance, and vision testing, insistence upon short olfactory tests has been traditionally the clinical norm, in many cases sacrificing sensitivity for expediency.

Types of Olfactory Tests Employed Clinically

This review focuses solely on psychophysical tests, i.e., tests that require a conscious response on the part of the patient and which relate private sensory experiences to antecedent physical stimulus properties. Papers which translate or change extant tests to other languages/cultures without significant alterations are not included, nor are tests focused on hedonics. Studies earlier than the 20th Century are not considered. Electrophysiological measures are not reviewed. Their use in clinic settings has been limited, given their current high cost, space requirements, and the need for trained personnel and relatively long test sessions. Moreover, they have yet to add insight into a patient's chemosensory disturbance. For example, they often do not detect function in patients with demonstrated psychophysical olfactory function.[12b] Imaging can be useful, although its applications are beyond the scope of this section of the document.

A large number of psychophysical olfactory tests have been introduced into the clinical literature and a number are well-established, practical, and have a strong scientific basis. Based on test length, complexity, and administration time they can be divided into "very brief tests" (i.e., <5 minutes administration time; **Table VIII.6**), "moderately brief tests" (i.e., 6-15 minutes of administration time; **Table VIII.7**), and "longer tests" (> 15 minutes of administration time; **Table VIII.8**). Because administration time can be influenced by the time subjects spend in making decisions and other factors these categories are heuristic and overlap in many instances. Moreover, a number of tests are self-administered so that their administration times are less critical from a practice management perspective.

Very brief tests are often used as simple screening tests that take only a few minutes to administer. They only suggest dysfunction and, when positive, should be followed by longer, more reliable, definitive tests. In most cases normative data, per se, are lacking for such tests, although cut-off values for defining abnormality are commonly noted. Some longer tests can differentiate degrees of dysfunction, e.g., anosmia, severe microsmia, moderate microsmia, mild microsmia, and normosmia, and have normative data based on age and sex. Short tests cannot make such fine distinctions. Decisions regarding which tests to use depend on the purpose of the intended test (e.g., for brief screening, more definitive clinical conclusions, research, etc.).

Table VIII.6. Very brief screening tests (administration times <5 minutes*)					
Test Name and Author(s)	**Test Type**	**No. of Odors or Items**	**Reliability Coefficient**	**Commercial Availability**	**Comments**
Le Nez du Vin McMahon and Scadding, 1996[43]	ID	6	NR	No	Six odorants selected from wine-tasting kit. Not sensitive to smoking or sex. Did differentiate between complainers and non-complainers of smell dysfunction. 0.79 correlation reported with UPSIT scores, but spurious due to score distributions.
Alcohol Sniff Test Davidson et al, 1997[44,45]	DT	1	0.80	No	Based on detecting alcohol pads at measured distances from nose; potential confound from trigeminal stimulation; uses ruler and alcohol wipes that are commercially available.
Kremer Olfactory Test Kremer et al, 1998[46]	ID	6	NR	No	Screening test based on spraying smell solutions into the oral cavity for retronasal evaluation and orthonasal comparisons with bottled solutions. No normative data. Normosmics outperformed hyposmics and anosmics
Four-Minute Odor Identification Test Hummel et al, 2001[47]	ID	12	0.78	Yes	Selected 12 odors from 16 on the basis of being correctly identified by 70% of > 1000 subjects. Statistically differentiated between normosmics, hyposmics, and anosmics but significant overlap between hyposmics and the other two groups. Score of 6 or lower highly suggestive of some olfactory

					dysfunction. May take more than 4 minutes.
3-Item Pocket Smell Test (3-PST) Duff et al, 2002[48]	ID	3	NR	Yes	A very rapid 4-alternative forced-choice screening test. Has been employed in a number of research studies and has been found to be differentiate between Alzheimer's disease and major affective disorder (depression).
Suprathreshold Intensity Ratings Koskinen et al, 2004[49]	IR	2, 3 conc each	NR	No	Rated intensity of 3 concentrations of vanilla and lemon aromas on a 9-point intensity scale. These ratings, unlike B-SIT and ETOC odor detection scores, did not differentiate between normosmic and hyposmic groups, but did differentiate anosmics from normosmics. Ratings fell on a different principal component than the other two, as observed by others.[18]
Quick Smell Test (Q-SIT) Jackman and Doty, 2005[50]	ID	3	0.87	Yes	A 3-item screening test with a no smell alternative. In 224 consecutive patients, this test identified abnormalities 99% of anosmics, as determined from the UPSIT. This number dropped to 85% for those with severe microsmia, 76% of those with moderate microsmia, and 50% of those with mild microsmia. Using a cut-off score of 2, the sensitivity and specificity of detecting anosmics was 99% and 40%, respectively.
Short Olfactory Screening Test	ID	5	0.77	Yes	Five odorants from the SS test chosen and compared to 20

Mueller and Renner, 2006[51]					descriptors. Scores of 4 and 5 "would be considered to be either normosmic or slightly hyposmic"; a score of 0 "might be anosmic or highly hyposmic". Non-forced choice with "undefinable odor" and "no odor" response alternative choices. Used in the National Social Life, Health and Aging Project survey.[52]
Odorized Marker Screening Test Vodicka et al, 2007[53]	ID	5	NR	NO	Employs commercially available colored children's odorized markers to dispense stimuli in a similar manner to that of the Alberta Smell Test[54] although different odorants and psychophysical procedures are used. Sum of points are assigned to initial "spontaneous naming" and then to a 4-alternative forced-choice identification task. Distinguishes anosmics from normosmics with high sensitivity and specificity. Requires blindfolding.
Parkinson Disease-Selective Odor Identification Test Bohnen et al[55]	ID	3	NR	Yes	Three UPSIT items identified with an accuracy of greater than 75% in differentiating Parkinson's patients from controls. Using a cut-off of 1 or less, diagnostic accuracy was 83.3% with sensitivity of 70.3% and specificity of 96.3%.
Short Connecticut Smell Test (CST) Toledano et al, 2009[56]	DT	1	NR	No	Single ascending method of limits threshold test using only n-butanol. Normal scores < 3 dilution number for subjects up to 50 years of age (n = 54) and < 4 for those over this age (n = 46). Validated by determining

					the sensitivity and specificity of differentiating persons with nasal polyposis from those without nasal polyposis.
Q-Sticks Test Hummel et al, 2010[57]	ID	3	NR	Yes	Determined the sensitivity and specificity of 3 odors to discriminate between anosmics, hyposmics, and normosmics, as defined by Sniffin' Sticks scores. Sensitivity and specificity of distinguishing anosmics from hyposmics/ normosmics were 98% and 59%.
OLFACT Smell Test Mullol et al, 2015[58]	DQ RQ ID	4	NR	No	Four[59] microencapsulated odorants presented with 3 questions: Do you detect this?; Do you recognize this? What is this (with 4 alternative names presented)? Analyzed from 9,348 surveys returned to investigators. Defined anosmia as not detecting any of the 4, normosmia detecting all 4, and hyposmia detecting 2-3 of the odorants.
4-Odor NHANES Pocket Smell Test Rawal et al, 2015 [60] Hoffman et al, 2016[61]	ID	4	NR	Yes	Expands 3-item Pocket Smell Test to 4 microencapsulated UPSIT odorants. 4-alternative responses in a folded cardboard format. Uses half of the 8 odorants employed in large National Health and Nutrition Survey (NHANES). See 8-item NHANES listing in Table 2.
6-Item Pocket Smell Test Christensen et al, 2017[62]	ID	6	NR	Yes	Selected PST odors easily identified by Europeans to assess sensitivity and specificity in differenting AD patients from controls and other

					patients with suspected dementia. Found test scores to aid in dismissing the diagnosis of probable AD although still had low sensitivity for detecting AD as such.
PREDICT-PD Smell Identification Test Joseph et al, 2019[63]	ID	5	NR	Yes	Established 4-item test from 23,232,278 combinations of UPSIT items that optimized differentiating patients with Parkinson's disease from normal controls. Subsequent approaches on a different dataset were similarly successful.[64]
Ethyl Alcohol Threshold Test Calvo-Hendriquez et al, 2020[65]	DT	1	NR	No	Provided five aqueous dilutions of ethanol (10% - 96%) on gauze strips next to one another. Task of 146 normal controls and 129 COVID-19 cases was to identify the weakest smell. Distinguished between these two groups. Requires preparation of stimuli.

*These times will vary depending upon the subjects. Some tests require preparation.

Abbreviations: DQ, detection question; DT, detection threshold; ID, identification; NR, not reported; RT, recognition threshold; RQ, recognition question. All tests are LOE 5.

Table VIII.7. Brief screening tests that have administration times 5-20 minutes*

Test Name and Author(s)	Test Type	No. of Odors or Items	Reliability Coefficient	Normative Data Available	Commercially Available	Comments
Blast Injection Test Elsberg and Levy, 1935[66]	RT	1	NR	NO	NO	Clinical application of test employing blast-injection of

						odors into the nose, with the metric being the minimum volume of odor that can be perceived. This procedure disassociated the stimulus from the variability associated with idiosyncratic aspects of sniffing or breathing and became popular in clinical medicine. Critics suggest confounding with trigeminal stimulation and other problems. Non-forced choice. Used mainly coffee odor as stimulus.
Phenyl Threshold Test Fordyce, 1961[67]	RT	1 at 8 Conc	No Coefficient; Reliability; shown as consistencies	NO	NO	Ascending non-forced-choice recognition threshold using wide-mouth sniff bottles. Reliability estimated from 98 subjects tested twice at intervals ranging from less than a day to 3

						weeks. Duration of intervals did not impact test scores which were higher on second test occasion.
Olfactory Spectrogram Douek, 1967[68]	DT	7	NR	NO	NO	Modified the blast-injection procedure of Elsberg[66] to include the 7 primary odors suggested by Amoore[69] into a practical clinical smell test. Employed increasing volumes of a in1/2 increments until a sensation was perceived. Non-forced choice...
Squeeze Bottle Olfactory Threshold Test Amoore and Ollman, 1983[70]	DT	1	0.70	Yes	No Longer	Employed propylene bottles with serial dilutions of pyridine in mineral oil to asses using an ascending method of limits olfactory thresholds. Later version employed linalool as a

						stimulus. Normative date available from the manufacturer. Widely used.
4-Odorant Method of Limits Threshold Test Eichenbaum et al, 1983[71]	DT	4	NR	NO	NO	Four ascending method of limits identification test with blank control on each trial based on 10 two-fold water dilutions of 4 odorants: almond (McCormick), ethanol (180 proof), lemon (McCormick) and acetone. Sniff bottles were employed. Score determined as highest dilution for which detection up to and including that dilution was errorless.
University of Pennsylvania Smell ID Test (UPSIT); aka Smell ID Test (SIT) Doty et al, 1984[72]	ID	40	0.94	YES	YES	Self-administered "Scratch & Sniff" 4-alternative forced-choice identification test. Norms based on 5 to 100 yr-old convenience

						sample of 3,928 persons; sex and age differentiation and percentile ranking[73]; sanitary; available in 36 language versions.
Yes-No Odor Discrimination Test Corwin, 1988[74]	DIS	20 (2 trials each)	0.69 (no. correct) 0.67 (d')	NO	NO	A yes:no identification test based 40 trials of 10 pairs of UPSIT items applicable to signal detection analysis, Provides a measure of odor identification and response bias. Shown to differentiate in the defining study patients before and after hemodialysis. No norms..
San Diego Odor Identification Test Murphy et al, 1992[75] and Markison et al, 1993[76]	ID	8	0.85[77]	NO	NO	Comprised of 8 non-standardized off-the-shelf common household odorants presented in opaque containers. Closed eyes recommended.

						Pictures of the 8 odorants and 12 distractors provided. Additional presentation of misidentified odorants given with feedback. Impairment defined as <6 odors being correctly identified
Odor Discrimination Test Smith et al, 1993[78]	DIS	16	0.43	NO	NO	Microencapsulated odorants presented in iso-intensive triads with one being different from the other two. Number correct of 16 trials is discrimination measure.
Suprathreshold Amyl Acetate Odor Intensity and Odor Pleasantness Rating Test Doty et al, 1995[31]	IR PR	1 odor; 4 Conc.	Mean IR: 0.76 Slope IR: 0.68 PR: 0.78	NO	YES	Employs 4 log concentrations of pentyl acetate and category ratings of intensity and pleasantness. Each stimulus presented 5 times. Both mean and slope of intensity functions serve as test

						measures, along with mean of pleasantness ratings. Has been employed mainly in studies of depression and schizophrena.
Brief Smell ID Test; aka Cross-Cultural Smell ID Test (B-SIT) Doty et al, 1996[79]	ID	12	0.73	YES	YES	Odors with international applicability; norms based on 5 to 100 yr old convenience sample of 3,760 subjects; sex and age differentiation and percentile ranks; self-administered; sanitary; availability of multiple test item versions.
Scandinavian Odor Identification Test Nordin et al, 1998[80]	ID	16	0.79	NO	NO	Comprised of 13 non-standardized off-the-shelf common household odorants and 3 essential oils presented in opaque containers. Forced-choice 4-

						alternative response set. Test correlates r = 0.76 with the UPSIT.
Jet Stream Olfactometer Ikeda et al, 1999[81]	ID	8	NR	NO	YES	A commercially available device that is suggested to overcome problems of the T&T olfactometer. Employs a standard stimulus pulse of 0.5 seconds and different concentrations of 3 of the 5 T&T odorants. Test scores correlated with the degree of nasosinus CT opacity in a small study cohort. Non-forced choice. Patients found test more difficult than the CCCRC detection threshold test with which is correlates.[82]
Smell Diskettes Briner and Simmen, 1999[83]	ID	8	NR	NO	YES	This screening test employs odorants embedded in 5 cm x 6 cm polyester

						diskettes that can be opened for testing and closed thereafter. Three response alternatives per odorant, which include both names and pictures. 102 normal subjects scored 7 (11) or 8 (91) on the test. 27 patients with olfactory complaints scored between 0 and 5 (mean 2.09)
Blast Injection Thresholds and Adaptation Time Tests Rydzewski et al, 2000[84]	DT RT ADAPT	2, Multiple conc	NR	NO	NO	Modified blast injection procedure of Elsberg and Levy in which detection threshold and identification thresholds are obtained based on volume of insufflated air required to produce responses. Also examines times for "olfactory exhaustion". Blast

						injection procedures widely criticized as confounding trigeminal and olfactory sensations and producing false positive responses.
Intensity Discrimination Test Öberg et al, 2002[85]	DISC	1 (6 conc	NR	NO	NO	Six concentrations of n-butanol presented in pairs with the task of differentiating the strongest of each pair. The weakest concentration was used as the standard. Four correct trials at a given concentration led to the next more difficult trial.
Odor Quality Discrimination Test Öberg et al, 2002[85]	DISC	4	NR	NO	NO	Four fruit-like odors presented in a 12-trial match to sample task (1 same, one different). Total score possible is 12. Source and names of odors not provided. .

Retronasal Powder Olfactory Identification Test Heilmann et al, 2002[86]	ID	20	0.76	NO	NO	Determined retronasal ability to identify odors. Four response alternatives per stimulus. Used grocery store condiments and powdered food items applied from squeeze bottles. Tap water rinses between trials.
Odor Memory/Discrimination Test Choudhury et al, 2003[87]	DISC OM	12	0.68	YES	YES	A 12-item, single-target, four-alternative, forced-choice test with 10, 30, and 60 sec delay intervals. Based on the Peterson-Peterson match-to-sample paradigm. Norms based on 106 men and 294 women spanning the age of 10 to 69 years.[88]
Unirhinal UPSIT Test Good et al, 2003[89]	ID	40	NR	YES	YES	Administered 20 UPSIT items to each side of in order to develop unilateral norms based on 270 subjects ranging in age from 15 to 64.

						Found no systemic left:right differences, although unilateral scores were below bilateral ones. Education correlated with left-side UPSIT scores only. Negative effects of smoking primarily in subjects with <12 years of education. Suggests unilateral norms may aid in following the development of some neurodegenerative diseases.
Odor Stick Identification Test Saito, 2006[90]	ID	13	0.77	NO	YES	Employs odorant microcapsules that are incorporated into lip stick-like creams that are applied to paraffin papers folded and rubbed together to produce scent. Employs identification with odor alternatives and both

						"detectable but not recognized" and "no smell" alternatives. Some smells not known to Americans.[91]
JOR Test Ahmad et al, 2007[92]	ID	10	NR	NO	NO	Ten odorants chosen to be easily identified by Jordanian subjects. Apparently only asked what they smell like without alternatives. Details of stimulus presentation procedure lacking. Reports Pearson correlation with UPSIT of 0.98 (Pearson), but this is misleading since half of the subjects were anosmic with Kallmann syndrome and half had high UPSIT (median: 37; mean 36.8; mode: 36).
Odorized Marker Screening Test Vodicka et al[53]	ID	5	NR	NO	NO	Employs commercially available colored children's odorized markers to dispense stimuli in

						a similar manner to that of the Alberta Smell Test[54] although different odorants and psychophysical procedures are used. Sum of points are assigned to initial "spontaneous naming" and then to a 4-alternative forced-choice identification task. Distinguishes anosmics from normosmics with high sensitivity and specificity. Requires blindfolding.
Connecticut Smell Test (CST) Toledano et al, 2009[56]	DT	1	NR	NO	NO	Single ascending method of limits threshold test using n-butanol. Normal scores < 3 dilution number for subjects up to 50 years of age (n = 54) and < 4 for those over this age (n = 46). Validated by determining the

						sensitivity and specificity of differentiating persons with nasal polyposis from those without nasal polyposis.
Short-term Odor Recognition Memory Test Zucco, 2011[93]	ID	16	0.90	NO	NO	A match-to-sample recognition test employing 16 target odors and various combinations of 16 foil odors using SS pens. Found to be sensitive to age but not sex. Similar to Odor Memory/ Discrimination Test of Choudhury et al[87] except microencapsulated odorants not used
Dusseldort Odor Discrimination Test Weierstall and Pause, 2012[94]	DIS	15	0.66	NO	NO	Based on extensive research of odorant mixture discriminations to optimize reliability relative to test length. Each stimulus is a mixture of 4 odorants selected from a total of 6 chemicals. In 102

						subjects, weak significant correlation ($p < 0.05$) with UPSIT ($r = 0.19$), but not with Sniffin' Sticks Discrimination Test ($r = 0.11$, ns).
Italian Olfactory Identification Test (IOIT) Maremmani et al, 2012[95]	ID	33	0.96	YES	NO	Employed Italian-specific microencapsulated odorants on white cardboard rectangles 35 x 55 mm). High reliability reflects inclusion of Parkinson's Disease and healthy normal data in the same analysis. Sensitive to sex and age. 95% cut-off reference limits provided for 3rd l-7th decades for each sex and both sexes combined.
Indian Smell Identification Test (INSIT) George et al, 2013[96]	ID	10	NR	NO	NO	Cotton balls dipped in commercially available essences from grocery store. Placed 1 cm

						in front of both nares. Four response choices per odor. Number of correct responses correlated well with Sniffin' Sticks 12-item odor ID test (r = 0.75) in subject group containing 53 normal and 50 Parkinson's disease subjects. Anosmia/hyposmic considered with score <5.[97]
NIH Toolbox Odor Identification Test Dalton et al, 2013[59]	ID	9 (adults) 5 (children)	0.58 (adults) 0.45 (children)	YES	YES	Scratch & sniff cards useful for testing adults and children. Normed on 1,446 children and 2,884 adults. Requires paid subscription for administration app and access to odorant cards. Follows age-related changes similar to those of B-SIT and UPSIT. Spanish version for 3-7 year olds has

						very low reliability (r = 0.20), but for adults is similar to that of English version (r=0.52).[98]
Open Essence Odor Identification Test Okutani et al, 2013[99]	ID	12	NR	YES	YES	Odorants presented in sealed envelopes that are released when opened. Six alternatives present for each odorant. In study of 176 medical students (median age 24 yrs), males exhibited median score of 10 and females a score of 11. Odorants designed for Japanese population.
15-Item Thai Smell Identification Test Chaiyasate et al, 2013[100]	ID	15	NR	NO	NO	Employed 15 non-standardized grocery store stimuli presented in glass bottles to 81 voluneers. Four response alternatives per odorant were presented. Percent correct responses noted >70% for 13

						of the 15 test items. No sex differences observed.
Olfaction Function Field Exam (OFFE) Kern et al, 2014[21]	ID DT	5 ID 2 Thresh	ID: NR Thresh: 0.56[101]	NO	NO	Employs abbreviated n-butanol and androstandienone (AND) threshold tests and a non-forced-choice 5-item odor ID test. Used in the National Social Life, Health, and Aging Project survey of 2,304 36-99 yr olds. Dysfunction defined as detecting 2 or fewer of the 5 odors in ID test and 4 or less of the 6 n-butanol concentrations. For AND, normosmics are those who detect all 4 concentrations, hyposmics 2 or 3, and anosmics one or none.

Retronasal Olfactory Test Croy et al, 2014[102]	ID	20	0.76	NO	NO	Used grocery store condiments and powdered food items applied from squeeze bottles. Tap water rinses between trials. Found significant differences in performance among cultures. Insensitive to age but not sex; differentiated between normal, hyposmic, and anosmic subjects determined orthonasally. Correlates with TDI Sniffin' Sticks orthonasal test 0.80.
Self-Administered Computerized Olfactory Testing System Jaing et al, 2015[103]	DT	1, 17 Conc	0.67	YES	YES	187 patients self-administer the computerized olfactory test system. Based on earlier threshold testing, a third were anosmic, a third microsmic, and a third normosmic. Correlation with

						squeeze bottle PEA threshold test was high 0.81, despite the reported test-retest reliability of 0.67. Age effects, but not sex effects, found.
8-odor NHANES Pocket Smell Test Rawal et al, 2015[60] and Hoffman et al, 2016[61]	ID	8	0.66-0.90	YES	YES	Comprised of UPSIT odorants contained in 2 folded Pocket Smell Tests of 4 odors each. Employed in large National Health and Nutrition Survey with multiple variables collected that can be empirically assessed. Dysfunction is defined as missing 3 or more of test items.
Sniffin' Test of Odor Memory (TOM) Croy et al, 2015[104]	OM	8	0.70	YES	NO	In this episodic memory tasks, subjects exposed to 8 odors and thereafter tested by a yes:no odor recognition task with the odors interspersed with

						8 other odors. Identification then determined. Both recognition and identification negatively impacted by age. Percentiles available for three age groups based on 96 subjects. An extended version of the test to 32 odors has been published recently without norms.[105]
Taiwan Smell Identification Test (TWSIT). Hsu et al, 2015[106]	ID IR	8	NR	NO	NO	A screening test using liquid stimuli. Categorizes dysfunction into normosmia, hyposmia, and anosmia based on points assigned to responses to questions of detection, recognition, and identification (total score of 50 possible). Validated on 187 subjects. Correlates 0.87

						with Traditional Chinese Language UPSIT.
Snap & Sniff® Odor Threshold Test Doty et al, 2018[107,108]	DT	1 odor; 15 concen-trations; 5 blanks	0.87	YES	YES	Employs 20 refillable smell "wands" that briefly expose odors within housings that eliminates possibility of wick directly touching the nose. Long odor retention. No blindfolds required. Validated on 736 clinic patients; norms based upon 414 subjects.
Snap & Sniff® Odor Discrimination Test Doty, 2019[109]	DISC	20	NR	YES	YES	Uses wands to be present odorants in sets of 3, with one odorant differing from the other two. Test score is the number of sets of 20 combinations that are correctly identified. Scores correlate 0.79 with UPSIT scores. Percentile ranks

						available for 41 healthy subjects.
Affordable Rapid Olfaction Measurement Array Test Villwock et al, 2020[110]	ID	14; 2 concen-trations each	0.85	NO	NO	Uses essential oils as stimuli. If subject detects a scent, a 4-alternative forced-choice odor identification task. Differentiates between normals and nasosinus patients. Correlates 0.75 with UPSIT.
Retronasal Powder Olfactory Identification Test II Yoshino et al, 2020[111]	ID	20	0.60	NO	NO	Oral "tasteless" flavor powders assessed retronasal function. Percentiles established within normal, hyposmic, and anosmic orthonasal tested groups. Only a two-point difference from 5th to 95th percentiles in normal group. Remarkably, test correlates higher than its own reliability values with Sniffin' Sticks

						tests (ID; 0.88; D: 0.84; Thresh: 0.77), likely reflecting distribution issues in which Pearson correlations should not have been used.
30-Odor Thailand Smell Identification Test Kasemsuk et al 2020[112]	ID	30	NR	NO	NO	In this study of 150 subjects, a 30-odor identification test applicable in Thailand was compared to the UPSIT and found a 0.64 correlation between the two tests.
*These times will vary depending upon the subjects. Some tests require preparation. Abbreviations: ADAPT, adaptation time; Conc, concentrations; DISC, discrimination; DT, detection threshold; ID, identification; IR, intensity rating; OD, odor memory; NR, not reported; PR, pleasantness rating; RT, recognition threshold. All tests are LOE5.						

Table VIII.8. Olfactory tests with administration times >20 minutes.

Test Name and Author(s)	Test Type	No. of Odors or Items	Reliability Coefficent	Normative Data Available	Commerciall y Available	Comments
9-Odor Ascending Threshold Test Proetz, 1924[113]	DT RT	9 with multiple dilutions	NR	NO	NO	Employed multiple concentrations of each of 9 odorants selected on the basis of chemical make-up, low

						trigeminal impact, and dynamic range in ascending non-forced-choice log-based threshold series. Rack designed to accommodate 100 bottles arranged in 10 rows making up a square.
Jones' Ascending Series Threshold Tests Jones, 1955[114]	RT	3 with 23 step dilutions each	n-butanol: 0.82 Safrol: 0.77 n-butyric acid 0.80	NO	NO	Sniff bottle and mineral oil dilutions of each of 3 odorants presented in counterbalanced fashion with each threshold being obtained six times for each odorant by 24 subjects. Blanks only used as comparison if subject not sure of sensation.
Henkin Olfactory Threshold Test Henkin and Bartter, 1966[115]	DT	2	NR	LIMITED	NO	Descending method of limits for pyridine and thiophene concentrations in both oil and water. A given forced-choice trial presented 3 stimuli, one odorant + carrier solution and carrier solution alone. 13 concentrations employed. Threshold defined as lowest

						concentration in which two successive correct responses occurred while two consecutive incorrect responses occurred at next lower concentration. Medians and ranges presented for 41 normal volunteers 6 to 59 years of age. Pyridine values at major variance from the Amoore Threshold Test.[116]
Short-Term Odor Memory Tests Engen et al, 1973[117]	OM	25 but different for individual subjects	NR	NO	NO	Demonstrated that short-term memory for odorants is associated with the number of response alternatives but that performance with retention intervals up to 30 sec is unimpaired. Among the first to provide a test of short-term odor memory.
n-Octanol Absolute and Difference Threshold Tests Rovee et al, 1973[118]	DT DIFF T	1 odor 17 levels	NR	NO	NO	For DT, ascending method of limits for 17 binary concentrations of n-octanol in diethyl phalate. Sniff bottles used. For DIFF T, 12.5% n-octanol used as standard followed by

						comparison concentration in ascending and descending trials. Sensitive to anxiety based on Taylor Manifest Anxiety Scale (40 college sophomore women selected from 160 on basis of anxiety scores..
T&T Olfactometer Toyota et al,1978[119] and Takagi, 1989[120,121]	DT & RT	5	DT: 0.56-0.71 RT: 0.33-0.45[31] (depends on odorant)	YES	YES	Filter paper strips dipped in bottles containing 8-log-step concentrations. Requires hood or other ventilation due to bad smell of some stimuli. Ascending method of limits with lowest concentration detected defined as detection threshold and lowest concentration with quality recognition threshold. Non-forced-choice. Norms not sex- or age-corrected, with 5 categories of dysfunction based on men and women 18 to 25 years of age.
Koelega Threshold Test Koelega, 1979[122]	DT	1 odor, 9 Conc.	0.65 bilateral;	NO	NO	Amyl acetate method of constant stimuli thresholds for 20 men

			0.51 Right; 0.59 left			and 20 women; no left:right differences found. College-age students; no determination of sex effects. No norms.
Ascending Pyridine, Thiophene and PEA Detection Threshold Tests Perry et al, 1980[123]	DT	3 odors, 19 Conc.	NR	NO	NO	3-Alternative ascending method of limits for each of 3 odorants presented in 125 ml Erlenmeyer flasks at 1 log steps. Total of 268 normal subjects tested. Age but not sex effects observed for thiophene and pyridine, but not phenyl ethanol.
Signal Detection Tests of Odor Sensitivity and Discrimination Potter and Butters, 1980[124]	SD	: 1 odor for sensitivity 8 odors for discrim	NR	NO	NO	Forced-choice method of signal detection used. For detection, 15 trials of odorant n-butanol and 15 trials of blanks. 4 category response report of certainty. For discrimination, 4 sets of 2 odorants each presented in 32 trials (15 with paired odorants (signal) and 15 with blanks (noise). Certainty of differences assessed. Tests shown

						to be sensitive to Korsakoff psychosis.
Amoore Threshold Test Sherman and Amoore, 1983[116]	DT	1 odor	0.70	YES	NO LONGER	Initially a 39-step binary pyridine dilution threshold series employing flasks. Later employed squeeze bottles and phenyl ethyl methyl ethyl carbinol.[70] Ascending series method of limits. Anosmia = inability to detect the 10th dilution step or lower of pyridine, hyposmia as detection of dilution steps 11-13, and normosmia as detection of steps 14 to 21. Sensitive to age and smoking.[125]
Connecticut Chemosensory Clinical Research Center (CCRC) Test Cain et al, 1983[126]	ID DT	10 ID 1 Thresh	ID: 0.60* Thresh: 0.68[127]	NO	NO	Comprised of an ascending forced-choice method of limits n-butanol squeeze-bottle threshold test plus identification test of 10 common non-standardized household items. Ammonia, Vicks vapor rub, and wintergreen are included as trigeminal stimulants. Response list of 20

						odorants used to cue subject responses.
4-Odorant Method of Limits Threshold Test Eichenbaum et al, 1983[71]	DT	4	NR	NO	NO	Four ascending method of limits identification test with blank control on each trial based on 10 two-fold water dilutions of 4 odorants: almond (McCormick), ethanol (180 proof), lemon (McCormick) and acetone. Sniff bottles were employed. Score determined as highest dilution for which detection up to and including that dilution was errorless.
Single Staircase Odor Detection Threshold Test Ghorbanian et al, 1983[128]	DT	1 Odor; 14 Conc.	0.88[31]	YES	YES	First use of staircase threshold procedure in olfactory studies; PEA odorant; propylene glycol diluent Sensitive to sex and age.[129] Later versions employed mineral oil diluent and squeeze bottles instead of sniff bottles held over nose.[130] Norms available only for more recent adaptations.[107,108]
Odor Confusion Matrix	ID	10	0.91[132]	NO	NO	Indicates that performance 80% or

Wright, 1987[131]						better reflects normality; attempts to explore confusions and thereby categorize dysosmias. Limited by the choice of odorants to which confusions can be made. % Correct correlates highly with UPSIT scores. Norms based on convenience sample 100 of persons.
Utrecht Odour ID Test Hendriks, 1988[133]	ID	18 or 36	0.68-0.77	YES	NO	Comprised of two subsets of 18 natural odorants designed for both the ORL clinic and industrial purposes. Odorants selected from larger set on the basis of familiarity to Dutch people. Norms provided for 221 normal controls but not divided in terms of age or sex.
Odor Discrimination/ Memory Test(s) Bromley and Doty, 1995[134]	OM and DISC	12	0.68[31]	NO	NO	Odor memory discrimination tests based upon (a) multiple target testing and (b) single target testing with 10, 30, and 60 sec delay intervals. The latter test has been shown to be age-

						and sex-related.[87] However, performance across these short-memory intervals is relatively constant, in accord with earlier studies.
Combined Olfactory Test Robson et al, 1996[135]	ID and RT	9 ID 1 Detect	0.87	NO	NO	Combined scores from a 9-odor identification test and an n-butanol threshold test for 133 subjects 12-80 yrs of age (mean 37.5). No indication of sex differences. No percentiles, but can be calculated from figures.
Sniffin' Sticks (SS) Test Kobal et al, 1996[136]	ID and DT	12, 16	ID:0.73, DT: 0.54 Comb: 0.72[34]	YES	YES	Norms based on 5- to 100-yr-old convenience sample of 9,139 subjects;[137] sex and age differentiation and percentile ranks; divides function into three classes; uses simple felt-tip marker pens to present stimuli. Later versions have 16 odors. Threshold reliabilities as high as 0.85 in later studies.[138]
Viennese Odor Test Lehrner and Deecke, 2000[139]	ID	20	0.75	NO	NO	A 20-odor identification test. Odors presented in plastic jars. Age-related

						normative sample based on 97 subjects. Raw scores converted to T-scores. T-scores below 30 indicative of smell loss. Combined with n-butanol threshold test
Random Olfactory Sensitivity Procedure Kobal et al, 2001[140]	ID	2 16 concentrations	0.71	NO	NO	Twelve concentrations each of phenyl ethanol and citronellal presented randomly with sum of correctly identified odors serving as test measure. Option of no smell provided, thereby making this test non-forced-choice. Correlates well with standard staircase threshold procedure (r = 0.77).
Odor Recognition Memory Test Öberg et al, 2002[85]	OM	48	NR	NO	NO	Subjects first presented with a set of 24 odors which they rated on familiarity, intensity, pleasantness, irritability, edibility). After a delay interval during wich other olfactory tests were performed, they were again presented with 24 odors, one at a

						time. Half were novel and half were in the original set. Had to report if each of the odors had been previously presented. Data subjected to signal detectionananalysis.
European Test of Olfactory Capabilities (ETOC) Thomas-Danguin et al, 2003[141]	ID and DT	16	0.90	?	NO	Test based on a combination of an odor identification and discrimination task. Uses a 4-alternative-forced choice procedure to first detect the odorant relative to 3 blanks and then indicate from 4 descriptors its quality. Measures are numbers of correct detection and identifications. Validated in France, Sweden and the Netherlands.
Biolfa® Olfactory Test Bonfils et al 2004[142]	DT and RT	3 and 8	----	NO	NO	Employs 9 aqueous concentrations each of 3 odorants to determine DTs using a forced-choice staircase procedure. Subjects were 67 normal and 155 patients with complaints of smell

						dysfunction. Eight odorants at four concentrations used for odor recognition performances.
Barcelona Smell Test Cardesin et al, 2006[143]	DT and RT	24	NR	NO	NO	Twenty CN I and 4 CNV odors presented in glass jars. Subjects asked (a) if they smelled something, (b) if they recognized the odor, and (c) to identify each odor from 4 response alternatives. In validation study, 120 subjects of a wide age range were on each side of nose separate and half on both sides together. ID better on left than on right side of nose. Females outperformed males. No normative data.
Odor Perception and Semantics Battery Luzzi et al, 2007[144]	DISC ON OPM	12	NR	NO	NO	Selected 16 odors from a larger set that are best known in Italy and England. Battery consists of a 16-paired same:different discrimination task using semantically-related odors (e.g., lemon-orange, petrol-paint, cocoa-coffee), an

						odor naming task, an odor-picture matching task, a word-picture matching task, and a picture naming task (control). Tests were differentially sensitive to several neurodegenerative diseases.
Candy Smell Test Renner et al, 2009[145]	ID	23	0.75	NO	NO	Uses hard sweet candies of unknown manufacturers to assess retronasal olfactory function in children and adults; scores correlate well with orthonasal smell tests. In 230 children and 123 adults, score of 13 or less differentiated anosmics from normosmics with a sensitivity of 94% and a specificity of 83%.
Extended Sniffin' Sticks Test Haehner et al, 2009[146]	ID DT DISC COMB	32	ID: 0.88 DT: 0.92 DISC: 0.80 COMB: 0.93	YES	YES	Extends Sniffin'Sticks individual subtests to a larger number of odorants to make them more applicable to individual testing and to increase their reliability. Found test-retest reliability no

						similar to that for established threshold measures, scores now sensitive to male:female differences and different degrees of smell loss.
Lyon Clinical Olfactory Test Rouby et al, 2011[147]	ID DT	ID: 16 Thresh: 2 5 Conc each	NR	NO	NO	Combines a 4-alternative forced-choice identification test (16 odorants) with two 5-concentration threshold tests (R-(+)-carvone (minty) and tetrahydrothiophene (additive to natural gas). Odorants presented in vials with mineral oil dilutions. Self-administered with supervision. No reliability coefficient reported, but binomial test of 20 subjects tested twice noted no meaningful differences.
Monell Extended Sniffin' Sticks Identification Test (MONEX-40) Freiherr et al, 2011[148]	ID	40	0.68	NO	NO	Added 24 odorants to the standard 16-item Sniffin' Sticks to provide a test comparable to the 40-item UPSIT. Administered to 259

						healthy young subjects, of which 72 were retested to assess reliability. Unlike original 16 Sniffin' Sticks, sensitive to sex. No normative data.
Smell-S and Smell-R Olfactory Tests Hsieh et al, 2017[149]	DT DISC	30	DT: NR DISC: 0.74	NO	NO	Employs mixtures of chemicals with different smells to assess odorant sensitivity and discriminability presented in glass jars or vials. Not meaningfully influenced by cultural factors. DT correlates with Sniffin' Sticks phenyl ethanol detection threshold 0.87.
Abbreviations: COMB, combination; DISC, odor discrimination; DIFF T, difference threshold; OD, odor discrimination; DT, detection threshold; ID, identification; OM, odor memory; ON, odor naming; NR, not reported; OPM, odor picture matching; RT, recognition threshold; SD, signal detection. All tests are LOE 5.						

Odorant presentation procedures range from simple "scratch & sniff" microencapsulated odorant labels, sniff bottles, atomizers, squeeze bottles, injection devices, and odorized wands, pens, and strips of filter paper dipped in odorant solutions to sophisticated olfactometers, including ones that automatically vary stimulus concentrations relative to subject responses. Both tests of baseline sensitivity (e.g., odor detection and recognition threshold tests, signal detection tests) and tests of suprathreshold function (e.g., tests of odor identification, discrimination, memory, hedonics, and build-up of odor intensity as odorant concentration

increases) have been described in detail in the clinical literature, with a number being available commercially. Each type of test has strengths and weaknesses. Moreover, as described below, some tests have been applied to, and in some cases specifically designed for, children (**Table VIII.9**). Concerns regarding sanitation suggest that some stimulus presentation procedures, most notably open sniff bottles, can be contaminated by successive uses by different subjects, a consideration in the age of COVID-19.

Table VIII.9. Olfactory tests designed for children

Test Name and Author(s)	Test Type	No. of Odors or Items	Reliability Coefficent	Estimated Test Duration	Normative Data Available	Commercially Available	Comments
San Diego Odor Identification Test Murphy et al, 1992[75,76]	ID	8	0.85[77]	~10 min	Limited	NO	Comprised of 8 non-standardized off-the-shelf common household odorants presented in opaque containers. Closed eyes recommended. Pictures of the 8 odorants and 12 distractors provided. Additional presentation of misidentified

							odorants given with feedback. Impairment defined as <6 odors being correctly identified
Rapid Screening of Identification Test for Children Richman et al, 1995[150]	ID	5	NR	< 5 min	Limited	NO	Administered 5 odorant ID test with different odors than that of their 1992 study to 825 children. Pictures of the 5 odors shown before the olfactory testing began to be certain that the children were aware of the odor sources. Demonstrated age and sex effects; high variability in scores. Suggested that a score of 3 or less in children over the age of 12 likely denotes olfactory dysfunction.
Match-to-Sample Odor Discrimination Test (MODT)	DISC	Multiple sets of 3-item tests (probe	NR	<15 min	No	NO	Tested 44 boys and 21 girls ranging in age from 2 to 18 years on a match-

Richman et al[151]		plus probe and distractor)					to-sample test. A 'probe' microencapsulated odor was first smelled followed by two odors placed in front of the child. The child indicated which one smelled like the probe. A total of 20 trials was performed. To vary the difficulty level for different age groups, 4 age-appropriate odorant sets were developed. The respective performances for 2-4, 5-9, 10-12, 13-15, and 16- to 18-year-old-subjects were 61%, 87%, 91%, 97% and 98%.
Odor Identification Test for Children Laing et al, 2008[152]	ID	16	0.45[59]	~ 5 min	Yes	NO	Employed 16 odorants presented in squeeze bottles familiar to most children. Administered test

							to 298 5- to 9-year olds. Four choices/odorant with pictures to aid in children's identification. Age-related norms based on 252 children and 56 adults. Cut-off points at 10th percentiles indicated for 5-, 6-, and 7-year olds, as well as adults. No differences between 3 child age groups; no sex effects.
Candy Smell Test Renner et al, 2009[145]	ID	23	0.75	~20 min	Limited	NO	Uses hard sweet candies of unknown manufacturers to assess retronasal olfactory function in children and adults; scores correlate well with orthonasal smell tests. In 230 children and 123 adults, score of 13 or less differentiated anosmics from

							normosmics with a sensitivity of 94% and a specificity of 83%.
NIH Toolbox Children's Test Dalton et al, 2011[153]	ID	6		< 7 min	Limited	Yes	Extensive developmental research to obtain 6 odorants familiar to children and could distinguish between those with normal smell or dyfunction in a low-cost, brief, easy to administer test. 1446 children were utilized to provide normative data that was validated against the UPSIT and B-SIT.
Pediatric Smell Wheel (PSW) Cameron and Doty, 2013[154]	ID	11	0.70	<5 min	Limited	Yes	Odorants are presented on a cardboard disk that rotates within an outer jacket, such that only one scratch & sniff odorant at a time is exposed for sampling. Pictures and words employed in game-like format.

							Can be self-administered. Validated on 152 children and adults; no normative data but scores below 5 suggestive of anosmia.
Test for Screening Olfactory Function in Children Dzaman et al, 2013[155]	ID	6	NR	<5 mi	Limited	NO	Six odorants chosen from a test of 21 odorants given to 37 children < 5 years old, 30 5-7 yrs old, and 18 7-10 yrs old. Odors presented in bottles. Score of 4 or more considered normal, being achieved by 96.5% of the 85 children.
Universal Sniff (U-Sniff) Test Schriever et al, 2018[156]	ID	12	0.83	<10 min	Yes	NO	Odorants selected to be identified by children [mean (SD) age; 6.3 (0.5) yrs]. Collaboration among 18 countries. Employs Sniffin' Stick pens to present stimuli. Forced-choice 4 response

							alternatives with pictures for each test item. Dysfunction based on 10th percentile which differed among some countries.
Paediatric Barcelona Olfactory Test Mariño-Sánchez et al, 2020[157]	ID DT	ID: 6 DT: 6 Concent	ID: 0.83 Thresh: 0.73	< 3 min	Limited	NO	A test for 6-17 yr old children based upon both an odor ID test and an ascending method of limits threshold test using T&T olfactometer protocol (initial detection, then recognition). Dysfunction defined by 10th percentile for both tests. ID: normal for 6-11 yr olds 4/6; for 12-17 yr olds 5/6). For threshold: 2/6.
Kradeo® Odor Identification Test Concheiro-Guisan et al, 2012[158]	ID	7	NR	<10 min	No	NO	Child required to name each of 7 odors without cues or response alternatives. Credit given to alternative names (e.g., Jasmine

							could be identified as “perfume” or “flowers” and mint as “chewing gum” or “toothpaste”. Calculated the percentage performance for each stimulus in 96 patients, 20 infected with SARS-CoV-2. Medians did not differ between these two groups.
Abbreviations: DISC, discrimination; DT, detection threshold; ID, identification; NR, not reported. All tests are LOE 5.							

Suprathreshold Olfactory Tests

Odor Identification Tests

As is apparent from **Tables VIII.6-9**, the most widely used clinical olfactory tests involve odor identification. Such tests have gained wide acceptance given that they are generally practical, reliable, easy to perform, economic of time and personnel, correlate with other types of tests, and, for subjects with no or minor smell loss, are the most enjoyable to take. Some are self-administered and can be sent to patients through the mail. Most are forced-choice, i.e., require indication of a specific odorant quality from a list of alternatives, although some include a “no odor” alterative. The latter makes it impossible to establish a likelihood of malingering based upon improbable response probabilities and to control for response biases (e.g., tendency to report the presence or absence of a smell independent of actual sensitivity), and can mitigate attending to subtle aspects of presented stimuli. Nonetheless, such tests are more accepted by persons who truly can’t smell, such as many elderly. Odor identification tests tap the full range

of olfactory deficits and all levels of the nervous system involved in olfactory processing. Their primary limitation is that some odorants are culture-specific, requiring different versions of tests for different cultures. Although generally well-correlated with other types of olfactory tests, notably threshold tests, for some diseases such as schizophrenia they are particularly sensitive to semantic processes that impact the ability to describe their sensations.[13]

Odor Discrimination Tests

In classical psychophysics, odor discrimination is defined as resolving power along a stimulus concentration continuum, reflecting the minimal increase needed to perceive a difference from a given odorant concentration.[14] A common index of this process is termed a just noticeable difference (JND or ΔS; also known as a Weber ratio), a value that is generally, but not completely, consistent across a range of concentrations of a given odorant. JNDs are sensitive to age and have been measured in clinical settings,[15] but have not been standardized.

A number of investigators define odor discrimination as the ability to differentiate between the quality of different odorants presented at suprathreshold levels. Such tests do not require overt identification of the stimuli, only a determination of whether or not they differ from one another in quality. In some tests, the task is to identify the "odd" or different stimulus in a series of stimulus presentations. When three stimuli are presented, two same and one different, this is commonly termed a triangle test. In other tests, a same:different response is obtained; e.g., two stimuli are presented on a given trial and the task is to report, for a given set, whether they are the same or different. Other tests require either matching an odorant to a sample or sorting odorants into specific categories. Still others have subjects rate the similarity of numerous odorants. Such similarity ratings are then assessed using sophisticated statistical algorithms that show the similarities and differences in multidimensional coordinates, with similar odorants falling into the same spatial regions. The latter tests require many trials and are rarely employed clinically. Moreover, most of these tests lack standardized normative data.

Odor Memory Tests

There are numerous types of tests designed to assess a patient's ability to remember and recall an odor. The most straight-forward of such tests simply add delay intervals between the inspection set and response set of an odor discrimination test. Clinically, it is most common that a single odorant is presented and the task is to identify that odor from a small set of odorants after different time delays. A dozen or more such "match-to-sample" trials is performed. Such tests were developed following the classical Peterson and Peterson short-term memory test for verbal material.[16] Other memory tests require a subject to smell a series of odorants (the "inspection set") and to pick out the odors from a larger set of odors presented at a later time. Unfortunately, in many memory tests it is the verbal label that is being remembered, e.g., "I recall smelling rose", rather than the specific odor, per se, which is well known and is present in long-term memory. In an effort to interfere with the verbal rehearsal of the inspection odor or odors, verbal tasks are often interspersed, with varying success, during the delay interval, such as counting backwards in threes from a large number. Attempts have been made to develop odor memory tests using stimuli that are not readily identified or categorized, although such tests have not been developed for clinical assessment. Odor memory tests have been shown to be more sensitive to effects of alcohol ingestion than odor identification tests and general threshold tests.[17] In general, however, short-term memory is rather robust and is only impacted by brain damage.

Odor Intensity Rating Tests

Numerous tests employ rating scales or other assessments of the build-up of perceived intensity as a function of increases in odorant concentration. Such tests appear to measure physiological processes somewhat separate from those measured by tests of odor threshold, identification, discrimination and memory.[18] The most common rating scales used clinically are category scales and visual analog or line scales. In category scaling, the perceived intensity is indicated according to specific categories (e.g., weak, moderate, strong); in visual analog scales, responses are placed along a line with such descriptors as "no smell" and "extremely strong smell" typically located at the ends of the line. Unfortunately, responses to such scales can be problematic and can lead to biased measures. For example, not all segments of the scale are

used by all subjects and bunching of responses at the higher end of the continuum commonly occurs. To minimize such problems, scales have been developed that provide logarithmic spaced descriptors at different points along the line to better mimic the known geometric progression of suprathreshold intensity sensations. More sophisticated procedures, such as cross-modal matching and magnitude estimation, provide more "ratio-like" response alternatives but are rarely used clinically for practical reasons, as reviewed elsewhere.[19] It should be noted that, unlike tests that require forced-choice responses (e.g., forced-choice questions in identification tests) or employ signal detection procedures, most intensity rating tests do not control for response biases.

Tests of Basal Odor Sensitivity

Odor Threshold Tests

Besides odor identification tests, the most widely used clinical olfactory tests involve discerning the lowest concentration of an odorant that can either be detected (detection threshold) or recognized (recognition threshold). Threshold tests are intuitively accepted by clinicians, regulatory agencies, and insurance companies given their similarity to widely-accepted auditory pure-tone threshold tests. Moreover, since they do not require language or knowledge of specific odors, they are not culture-dependent and their scores can be directly compared among different cultures. However, compared to identification tests, they require more administration time, are typically of lower reliability, and are limited in terms of the spectrum of odorants that can be evaluated. Despite the fact that variations in intertrial intervals do not meaningfully impact threshold values, the procedures used to present the odorants, such as volumes of sniff bottles, do have such impact.[20] Although, in general, persons with high thresholds (i.e., low sensitivity) to one odorant tend to have high thresholds to other odorants, and vice versa, this is not the case with all odorants. This is particularly evident for odorants for which some people are relatively insensitive (i.e., so-called specific anosmias). Unfortunately, the concepts of detection and recognition are commonly confounded in threshold test procedures (e.g., having a subject smell a higher concentration of a threshold series so the odor can be identified and then claiming detection thresholds are being measured), thereby

increasing variability.[21] Failure to provide specific instructions can lead to such confounding. Threshold tests can be frustrating for patients given that many trials are weak or below threshold, leading even those with a normal sense of smell to believe they performed poorly on the test.

It is commonly stated that threshold tests are solely a measure of peripheral, i.e., epithelial, olfactory function. However, this is clearly not the case. Even detection threshold tests require cognitive processes such as working and short-term memory (e.g., discerning a stimulus from blanks in a temporal sequence[22]) and are impacted by top-down centrally-mediated decision processes.[22] Indeed, threshold tests, like tests of odor identification and discrimination/memory, have been shown to correlate with neuropsychological measures of verbal and visuospatial memory.[23] Importantly, threshold measures are sensitive to lesions in higher order brain structures such as those observed in Alzheimer's disease,[7] multiple sclerosis,[24] and epilepsy.[25] Moreover, given the greater variability and lower reliability of most threshold tests compared to identification tests, observations of weaker cognitive associations with threshold tests than with identification tests do not necessarily imply a meaningful differential cognitive load.

Methods to obtain threshold measures vary, and, despite assumptions often made by regulatory agencies, there is no single threshold value for a given odorant. Hence, like other psychophysical measures, threshold values depend upon the procedures employed in estimating them and multiple subject factors including age and sex. In the method of constant stimuli, a range of odorant concentrations are randomly presented and an ogive-like function (cumulative frequency graph) is fitted to the stimulus-response function (concentrations on the abscissa and performance, e.g., percent trials that are correct, on the ordinate). When a blank comparison is provided at each concentration in a forced-choice task, the concentration where 75% performance occurs is commonly calculated as the threshold, since by chance alone 50% of the trials would be performed correctly. Although this method can also provide information about an odorant's psychophysical dynamic range, i.e., the sharpness of the build-up in performance across a given concentration gradient, only rarely is the method of constant stimuli used clinically. This is due to the need for a large number of trials to obtain a reliable

measure. Nonetheless, this is the gold standard method to which other threshold tests are commonly compared and there are a few clinical applications of this technique. In the initially ascending methods of limits procedure, stimuli are started at below-threshold concentration levels and then increased in concentration until they are detectable. Repeated trials are required. This approach has been codified as the ASTM International E679 procedure.[26] Versions of this procedure have employed methods to blast boluses of odorants into the nose to minimize impact of sniffing or breathing, so called blast injection technique. In initially ascending series staircase procedures, stimuli are increased in concentration from below threshold levels systematically until they are detected then decreased and increased according to the correctness of subject responses within the perithreshold region. An average of the reversals, i.e., points of upward or downward transitions provides the threshold estimate. Although double staircase procedures,[27] i.e., procedures in which two staircases are performed simultaneously (one initially descending from higher concentrations and the other initially ascending from lower concentrations) are commonly used in other sensory systems and are generally preferable,[28,29] they are rarely employed in olfaction due to time considerations and concerns about adaptation. In general, staircase procedures are preferred over other methods, resulting in relatively stable and reliable thresholds with a minimum number of trials.[30]

Signal Detection Tests

Signal detection tests require subjects to differentiate between low levels of an odorant, usually a single concentration established for each subject separately, and blank stimuli, although subtle quality differences between stimuli also can be measured. Instead of conceptualizing sensitivity as a border between no sensation and sensation, as occurs in threshold measurement, signal detection theorists view the detection task as discriminating between noise and signal plus noise. Signal is viewed largely as a constant, whereas noise reflects physiological and psychological variations of the subject, including the liberalness or conservativeness of the subject at any one time in reporting the presence or absence of the signal, i.e., the subject's response criterion. The advantage over threshold testing is that signal detection analysis can independently differentiate a subject's response criterion from his or her

sensitivity, per se. Thus, a more emotional subject may believe that they perceive a stimulus but the response actually reflects greater liberalness in reporting its presence. Such tests are exquisitely sensitive to very subtle deficits in smell function, but typically take more time than threshold tests given the large number of trials needed for stable measures and the need to titrate the stimulus concentrations for each subject. Moreover, normative data for olfactory signal detection tests are lacking. Some shorter signal detection tests have been employed clinically.

Reliability of Olfactory Test Measures

In general, the more items or trials in an olfactory test, the higher its reliability, i.e., measurement consistency over time.[31] Reliability is a prerequisite for validity. However, reliability coefficients, which are the main measure of such consistency among subjects of a group, depend upon the variation in test scores and can be misleading when distributions of scores are restricted, e.g., by being grouped into too few categories. Although test-retest reliability coefficients are reported for numerous tests, differences among such coefficients are rarely assessed for statistical significance. In a study in which this was done, the reliability coefficients of tests that ranged from 0.90 to 0.76 did not differ significantly from one another.[31] These coefficients did differ from those ranging from 0.71 to 0.67, which in turn differed significantly from those ranging from 0.53 to 0.43. Hence, when subtle differences in reliability coefficients are reported among tests, one cannot assume that the differences are statistically meaningful. That being said, reliability coefficients are among the few metrics to which tests can be compared and, despite confounding factors, need to be considered, in context, when choosing a test for administration. Reliability coefficients are a guide, but not the sole determinate of the value of an olfactory test and comparisons across tests can be enigmatic. As can be seen in **Table VIII.6**, of 73 tests that were surveyed, a significant number failed to provide this very basic psychometric measure.

Relationships Among Nominally Different Types of Olfactory Tests

In general, tests of odor identification, detection, discrimination, and memory are correlated with one another (**Table VIII.10**), with the sizes of the correlation being theoretically bound by the less reliable test and the range of test scores used in the computation. Because of such relationships, many authors default to the most reliable of the tests as the only needed indicator of smell function. While a case can be made that nominally different tests may be differentially sensitivity to a number of disorders, for most practical purposes more than one type of test is not needed.

Table VIII.10. Correlations among extant psychophysical olfactory tests

Study Author(s)	Mean (SD or range) Age	No. of Subjects Sex M/F	Subject Type	Correlated Tests	Correlation Coefficients	P
Doty et al, 1984[72]	42.4 (18.9)	64 M and F	Healthy	UPSIT vs. Threshold (PEA)	0.89	0.001
			Healthy minus anosmics	UPSIT vs Threshold (PEA)	0.79	0.001
Stevens and Cain, 1987[159]	77 (70-90)	NR	Healthy	Identification vs Threshold (iso-amyl butyrate)	0.51	0.02
				Identification vs. Threshold (benzaldehyde)	0.56	0.006
				Identification vs Threshold (d-limonene)	0.63	0.003
	21.0 (18-24)	NR	Healthy	Identification vs Threshold (iso-amyl butyrate)	0.30	NS
				Identification vs. Threshold (benzaldehyde)	0.21	NS
				Identification vs Threshold (d-limonene)	0.16	NS

Cain et al, 1988[160]	47.2 (6-85)	670 (NR)	Mixed and S&T patients	Identification vs Threshold (n-butanol)	0.77	0.001
Cain and Rabin, 1989[161]	1: 46.5 (9-75) 2: 44.6 (18-33)	24/26 22/36	S&T Clinic Patients	UPSIT vs butanol threshold (2 sessions w/diff subjects; 4 and 5 trial correct response criterion for thresholds of each session)	0.92, 0.96	0.001
				UPSIT vs CCCRC ID test	0.95, 0.96	0.001
				Butanol threshold vs CCCRC ID test	0.73, 0.90	0.001
Cain and Gent, 1991[127]	37.3 (NR)	10/22	Healthy	pyridine threshold vs. butanol threshold	0.74	0.001
				pyridine threshold vs. isoamyl butyrate threshold	0.86	0.001
				pyridine threshold vs. phenylethylmethylethyl carbinol (PEMEC) threshold	0.69	0.001
				Isoamyl butyrate threshold vs PEMEC threshold	0.86	0.001
				Isoamyl butyrate threshold vs butanol threshold	0.71	0.001
				Butanol threshold vs PEMEC threshold	0.66	0.001
Doty et al, 1994[18]	45.8 (20.2)	37/60	Healthy	UPSIT vs Butanol Threshold Test	0.41	0.001
				UPSIT vs T&T Detection Threshold Test (composite)	0.41	0.001
				UPSIT vs T&T ID Test (composite)	0.61	0.001

				UPSIT vs. Yes:No Discrimination Test	0.60	0.001
				UPSIT vs. Odor Intensity Rating Test (slope)	0.29	0.001
				UPSIT vs Odor Intensity Rating Test (mean)	0.27	0.001
				UPSIT vs. PEMEC Threshold Test	0.49	0.001
				UPSIT vs PEA Threshold Test (scaling factor reversed)	0.63	0.001
				UPSIT vs Odor Discrimination Test	0.59	0.001
				UPSIT vs Odor Memory Test	0.62	0.001
Hummel et al, 1997[162]	49.5 (18.5)	55/52	Healthy	SS Odor Identification vs SS Threshold (butanol)	0.54	0.001
				SS Odor Identification vs SS Discrimination	0.56	0.001
				SS Threshold vs SS Discrimination	0.66	0.001
				SS Odor Identification vs CCCRC Identifcation	0.50	0.001
				SS Odor Identification vs CCCRC Threshold (butanol)	0.24	0.001
				SS Odor Threshold vs CCCRC Identifcation	0.38	0.001
				SS Odor Threshold vs CCCRC Threshold (butanol)	0.34	0.001
				SS Odor Discrimination vs CCCRC Identification	0.35	0.001
				SS Odor Dis[34]crimination vs CCCRC Threshold	0.31	0.001
				CCCRC Identification vs CCCRC Threshold	0.29	0.001

Nordin et al, 1998[80]	(15-79)	21/21	Healthy	UPSIT vs Scandinavian Odor-Identification Test	0.76	0.001
				CCCRC Threshold Test vs. Scandinavian Odor ID Test	0.60	0.001
Lehrner et al, 1999[163]	38.4 (18-90)	31/65	Healthy	Odor Identification vs n-butanol Threshold	0.31	0.01
				Odor Identification vs Odor Memory	0.69	0.01
				Odor Memory vs n-butanol Threshold	0.31	0.01
Seeliger et al, 1999[164]	19-61	22/17	Usher Synd.	SS Identification vs SS Discrimination	0.09	NS
				SS Identification vs SS Threshold (butanol)	0.01	NS
				SS Discrimination vs SS Threshold (butanol)	0.14	NS
Kobal et al, 2001[140]	47.0 (19-78)	45/52	S&T Cinic Patients	Random Test vs. SS Discrimination	0.71	0.001
				Random Test vs SS Threshold (butanol)	0.77	0.001
				Random Test vs. SS Identification	0.74	0.001
				SS Identification vs SS Discrimination	0.79	0.001
				SS Identification vs SS Threshold (butanol)	0.75	0.001
				SS Discrimination vs SS Threshold (butanol)	0.69	0.001

Koskinen et al, 2004[49]	49.5 (15-84)	15/33	S&T patients	SS Threshold (butanol) vs. SS Odor Discrimination	0.25	NS
				SS Threshold (butanol) vs SS Odor Identification	0.44	0.01
				SS Threshold (butanol) vs Brief Smell Identification Test	0.42	0.01
				SS Threshold (butanol) vs ETOC Odor Detection	0.34	0.05
				SS Threshold (butanol) vs ETOC Odor Identification	0.31	0.05
				SS Threshold (butanol) vs Odor Intensity	0.19	NS
				SS Odor Discrimination vs SS Odor Identification	0.53	0.01
				SS Odor Discrimination vs Brief Smell Identification Test	0.54	0.01
				SS Odor Discrimination vs ETOC Odor Detection	0.37	0.05
				SS Odor Discrimination vs ETOC Odor Identification	0.59	0.01
				SS Odor Discrimination vs Odor Intensdity	0.43	0.01
				SS Identification vs Brief Smell ID Test	0.83	0.01
				SS Identification vs ETOC odor detection	0.79	0.01
				SS Identification vs ETOC odor identification	0.85	0.01
				SS Identification vs Odor Intensity	0.64	0.01
				Brief Smell ID Test vs ETOC Odor Detection	0.73	0.01
				Brief Smell ID Test vs ETOC odor identification	0.82	0.01

				Brief Smell ID Test vs. Odor Intensity	0.56	0.01
				ETOC Odor Detection vs ETOC Odor Identification	0.84	0.01
				ETOC Odor Detection vs Odor Intensity	0.66	0.01
				ETOC Odor Identification vs Odor Intensity	0.57	0.01
Tsukatani et al, 2005[82]	38.1 (15.6)	30/45	S&T patients	Jet Stream Olfactometer Recog Threshold vs CCCRC Identification Test	0.78	0.01
				Jet Stream Olfactometer Detect Threshold vs CCCRC Threshold Testt	0.68	0.01
Kobayashi et al, 2007	55 (16)	23/27	S&T patients	Odor Stick Identification Test (13, 11, 8 items) vs CCCRC ID Test	0.80, 0.82, 0.83	0.001
				Odor Stick Identification Test (13, 11, 8 items) vs CCCRC Threshold Test	0.74, 0.76, 0.76	0.001
				Odor Stick Identification Test (13, 11, 8 items) vs CCCRC Composite	0.80, 0.82, 0.83	0.001
Luzzi et al, 2007[144]	71 (8)	7:7	Alzheimer	Odor Naming Test vs Odor-Picture Matching Test	0.64	0.01
	64(7)	8:3	Frontotemporal Dementia	Odor Naming Test vs Odor-Picture Matching Test	0.85	0.001
				Odor Discrimination Test vs Odor Naming Test	0.75	0.01
				Odor Discrimination Test vs Odor –Picture Matching Test	0.78	0.005

Tourbier and Doty, 2007[165]	59.7 (15.6)	51:81	S&T patients	UPSIT vs. odor detection threshold (PEA)	0.84	0.001
				UPSIT vs odor discrimination/memory test	0.67	0.001
				Odor detection threshold (PEA) vs. Odor Discrimination Memory Test	0.64	0.001
Lötsch et al, 2008[166]	35.2 (16.2)	916/1160	S&T Patients	SS Identification vs SS Discrimination	0.26	0.001
				SS Identification vs SS Threshold (butanol)	0.28	0.001
				SS Discrimination vs SS Threshold (butanol)	0.26	0.001
Hedner et al, 2010[33]	57.2 (13.8)	64/106	Healthy	SS Identification vs SS Discrimination	0.22	0.01
				SS Identification vs SS Threshold (butanol)	0.17	NS
				SS Discrimination vs SS Threshold (butanol)	0.24	0.01
Hong et al,[167]	40.87	128/83	Healthy & S&T Patients	Korean Identification score vs T&T recognition threshold score	0.58	0.01
				Korean TDI sum score vs T&T recognition threshold score	0.73	0.01
				Korean threshold score vs T&T detection threshold score	0.66	0.01
Mahmut et al, 2012[168]	20 (NR)	39/40	Healthy	SS Identification vs SS Discrimination	0.28	0.001

				SS Identification vs SS Threshold (butanol)	0.34	0.001
				SS Discrimination vs SS Threshold (butanol)	0.28	0.001
Weierstall and Pause, 2012[94]	23.5 (3.7)	52/0	Healthy	Disseldorf Odour Discrimination Test vs UPSIT	0.19	0.05
				Disseldorf Odour Discrimination Test vs		
				UPSIT vs S&S Discrimination	0.25	0.01
Soler et al, 2016[169]	52.7 (16,1)	49/61	Rhinosinusitis	SS Identification vs SS Discrimination	0.70	0.001
				SS Identification vs SS Threshold (butanol)	0.69	0.001
				SS Discrimination vs SS Threshold (butanol)	0.62	0.001
Doty et al, 2019[107]	58.0 (16.10)	327/409	S&T patients	UPSIT vs. Snap & Sniff® Threshold Test (PEA)	0.65	0.001
				UPSIT vs Smell Threshold Test (PEA)	0.63	0.001
				Snap & Sniff® Threshold Test (PEA) vs. Smell Threshold Test (PEA)	0.67	0.001
Kasemsuk et al, 2020[112]	42.7 (15-84)	38/112	112/38	UPSIT vs 30-item Thai Odor Identification Test	0.64	0.001

Aniteli et al, 2020[170]	20-80	100	Healthy and S&T Patients	CCCRC Odor ID test vs Brief Smell Identification Test (B-SIT) Right Nostril	0.90	0.001
				CCCRC Odor ID test vs Brief Smell Identification Test (B-SIT) Left Nostril	0.90	0.001
Abbreviations: CCCRC, Connecticut Clinical Chemoreception Research Center; PEA, phenyl ethyl alcohol; SS, Sniffin' Sticks; S&T, Smell and Taste; UPSIT, University of Pennsylvania Smell Identification Test.						

Despite their being correlated, comparison of results from nominally distinct tests must be interpreted conservatively, since different psychophysical tests rely on several odorants at variable concentrations, have different cognitive demands[32,33] and vary in terms of their reliabilities.[31,34] In one study employing Sniffin' Sticks felt-tip pen markers to present stimuli, demographic and cognitive factors accounted for 15% of the variance in odor identification values, 23% of the variance of discrimination values, and 9% of the variation in threshold values.[33]

It is important to recognize that operational terms used to describe olfactory tests (e.g., detection, identification, discrimination, memory) are not pure representatives of independent physiologic or psychologic chemosensory processes signified by their names.[18] The correlations among such tests are a testament to this fact (**TableVIII.10**). For example, if an odor is to be identified or remembered, it must first be detected. The ability to remember odor qualities is a prerequisite for discriminating among them, assuming they are of equivalent intensity. Discrimination requires discerning odor qualities although identification is not required. As noted earlier, even threshold tests rely on some level of cognitive processing.

Unilateral or Bilateral Testing?

In general, bilateral tests reflect the better functioning side of the nose and for this reason are not sensitive to unilateral deficits. Testing each side of the nose is useful for detecting deficits confined to one side of the nose, although in most cases deficits are bilateral and unilateral testing can be confounded by the nasal cycle which impacts airflow in some persons to the olfactory cleft. A common way to test each side of the nose separately is to occlude the non-

tested side with a piece of tape. Microfoam tape (3M Corporation, Minneapolis) is commonly used since it is odorless, easy to apply and remove, and leaves no residue. Normative unilateral data are available for some tests.

General Recommendations

The choice of an olfactory test depends upon the purpose that is intended. In general, forced-choice tests of odor identification are preferred to other types of tests based upon reliability, their correlation with other types of tests, and practicality. A number can be self-administered, minimizing physician involvement and personnel costs. In the era of COVID-19, throw-away identification tests may have the advantage of minimizing the likelihood of instrument contamination and viral spreading from breathing on test instruments.

Although very brief screening tests (e.g., 4 items) can be used to roughly screen for smell loss, longer tests are recommended to minimize the likelihood of obtaining false negative and false positive responses. Shorter screening tests can only assess the presence or absence of dysfunction and do not make it possible, in individual cases, to detect probable malingering or to accurately establish clinically useful degrees of dysfunction. This is a major limitation as decreased smell function in the absence of anosmia can be a significant liability and patients need to be counselled regarding their perceived smell problem and the degree of their deficit.

Threshold tests are generally less reliable and are more time consuming than identification tests, but when done properly correlate well with them. As with identification tests, forced-choice responding should be employed. There is controversy whether threshold and other types of olfactory tests add anything to identification tests. Reliability, and thus sensitivity, is increased when test results of nominally different test measures are combined. The most appropriate statistical approach for doing this is to first to convert them to z-scores or other appropriate metrics and implement well-established statistical methods that take into account scale differences and test reliabilities, as described elsewhere.[35] Interpretation of such conglomerates, however, is difficult because the relation contributions of different types of tests are not possible, so the test measures must be viewed as heuristic. Blast injection tests are not recommended for threshold stimulus presentation, as they confound trigeminal

stimulation with olfactory sensitivity, fail to take into account normal aspects of sniffing, and do not have strong normative support of clinical value.

Rating scales and analogous forms of suprathreshold tests (e.g., magnitude estimation) are not recommended as sole measures of smell function largely because of their dependence on stimulus range,[36] susceptibility to context effects,[37] lack of normative data, susceptibility to memory factors,[38] and lesser sensitivity to olfactory dysfunction associated with age[39] and a number of diseases (e.g., schizophrenia[40]). Although there are proponents of magnitude estimation (e.g., where numbers are assigned in proportion to the relative degree of intensity), more practical procedures such as labeled magnitude scales, in which verbal descriptors are placed along the scale in a seemingly ratio-like manner, have become popular.[41] However, such scales have inherent limitations that most likely impact the comparison of their results between subjects.[42]

Among the tests evaluated in this section, a number exhibit acceptable reliability and some are commercially available. Because of standardization and literature support, including normative data, we recommend that commercially available tests be considered for general use. However, some non-commercial tests are easy to fabricate and therefore if staff are available for preparing them they can be appropriate as well, although normative data are largely lacking. Nonetheless, despite the availability of general normative data, collection of local norms is encouraged for research studies in which subtle effects are expected or cultural factors may impact study outcomes.

SECTION: VIII. Evaluation and Diagnosis

D. Use of validated survey QOL testing

Olfactory-specific quality of life (QOL) can be assessed by multiple methods including survey responses, symptom scores, and visual analog scales (VAS).[1] Often, these patient-reported methods supplement quantitative olfactory testing. Several instruments have been described and validated, including the Questionnaire of Olfactory Disorders (QOD),[2] the Assessment of Self-Reported Olfactory Function and Olfaction-Related QOL,[3] the Multi-Clinic Smell and Taste

Questionnaire-Scandanavian (MCSTQ-Sc),[4] and other QOL-based surveys.[5] These surveys generally provide information regarding the degree to which patients suffer from OD. The QOD is the most commonly used metric, of which the most frequently employed version incorporates 17 negative statements (QOD-NS).[1] The QOD has high consistency, reliability, and validity.[1] Thresholds of clinical relevance exist for this instrument.[6]

Beyond validated questionnaires, non-validated means have been employed to ascertain olfactory QOL. Studies in various fields including CRS, biologics, septorhinoplasty, and skull base surgery have used the single question from the SNOT-22 survey on "Decreased sense of smell/taste."[7–10] While the intent of this is admirable, caution should be applied when interpreting results from this approach, as factors such as the "halo effect" can lead to spurious findings.

In patients with CRS, olfactory QOL and quantitative olfactory testing results generally correlate, although this association is mixed among populations without sinonasal disease and potentially in those treated with medical therapy for CRS. A prospective study of 121 subjects with CRS identified a moderate correlation between QOD and 40-question Smell Identification Test findings (r=0.40).[11] OD identified via the Sniffin' Sticks Test (SST) is associated with worse QOD-NS scores among subjects with CRS, with ROC analysis yielding a sensitivity of 60.9% and specificity of 81.8% for the QOD-NS to detect quantitative OD.[12] Alternatively, after medical treatment of CRS, improvement in SST was not associated with QOD-NS scores (r=-0.016) on short-term follow up.[13] In a community-based sample of 7,267 individuals, negligible associations were identified between SST results and general health QOL surveys.[14] However, other studies in dysosmic adults and in patients with post-infectious, post-traumatic, sinonasal, and idiopathic OD show that QOD scores were generally associated with SST findings.[15,16]

Among patients with CRS, olfactory-specific QOL is further impaired in those with nasal polyps and comorbid allergy.[11,17] Deficits on the QOD-NS have been associated with worse economic and productivity metrics in patients with CRS.[18] Patients who underwent both surgical and medical treatment of CRS have reported improvements in QOD-NS scores.[11,13,17]

Many studies on OD during the COVID-19 pandemic have been conducted. The majority of these studies at the time of writing utilize VAS or non-validated questionnaires when

assessing patient-reported OD, though some employ the QOD. A prospective study of 81 patients with COVID-19 demonstrated that self-reported olfactory loss assessed via VAS was predictive of abnormal quantitative olfactory function.[19] An international series employed the QOD along with VAS and concluded that olfactory or gustatory dysfunction may represent early symptoms of infection.[20] A series of patients with mild COVID-19 infection demonstrated elevated QOD scores, which correlated with impaired psychophysical olfactory testing and gustatory dysfunction.[21]

Validated olfactory QOL questionnaires have been applied to other populations with OD. In a cohort study of adult patients without otolaryngologic complaints, QOD scores were elevated and associated with metrics of loneliness.[15] Patients with anosmia and hyposmia had impairments on the MCSTQ-Sc.[22] A multi-national study of patients from Smell and Taste Clinics demonstrated that those with post-infection and post-traumatic OD had worse olfactory-specific QOL than those with sinonasal and idiopathic OD.[16]

The impact of OD is broad and extends beyond olfactory-specific realms. Patients with OD often describe anhedonia, frustration, sadness, and isolation.[23] In addition to olfactory-specific QOL deficits, individuals with OD from both CRS and non-CRS etiologies have impairments in areas including general health-related QOL, depression, loneliness and productivity loss.[15,17,18]

Table VIII.11 Section Evidence Summary Table: Use of Validated Survey QOL Testing

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Soler et al[11]	2016	3	Prospective cohort	121 patients with CRS who underwent ESS	1) QOD-NS 2) SIT-40	Olfactory QOL worse with polyps and asthma Baseline QOD-NS and SIT-40 scores had moderate correlation

Mattos et al[12]	2017	3	Prospective cohort	109 patients with CRS	1) QOD-NS 2) SST 3)Correlations between olfactory metrics and patient/disease factors	QOD-NS correlates with TDI, SNOT-22. QOD-NS can screen for OD based on ROC analysis
Thomas et al[13]	2020	3	Prospective cohort	48 patients with CRS treated medically, short-term follow up	1) Endoscopy scores 2) SST 3) QOD-NS 4) SNOT-22	Medical treatment of CRS was associated with short-term improvements in olfactory QOL, without improvement in olfactory function Olfactory function did not associate with QOL measures
Hinz et al[14]	2019	3	Cross sectional, community-based	7,267 individuals not screened for CRS	1) SST 2) SF-8 3) GAD-7 4) LOT-R 5) SWLS	Negligible associations were identified between OD and QOL across multiple non-olfactory QOL metrics in a community (non-CRS) population.
Katotomichelakis et al[17]	2014	3	Prospective cohort with control arm	111 patients with CRS who underwent ESS 48 healthy subjects	1) SST 2) QOD 3) BDI 4) SF-36	OD and polyp status were associated with improvement in all QOL measures after ESS
Schlosser et al[18]	2017	3	Prospective cohort	221 patients with CRS	1) SST 2) QOD-NS 3) Associations between olfactory measures and healthcare use,	Impaired olfactory QOL is associated with worse economic and productivity measures and greater medication use

					productivity and medication use	
Prajapati et al[19]	2020	3	Prospective cohort study	81 patients with COVID-19, 54 of whom reported smell loss	1) Olfaction scores via VAS 2) 12-Item BSIT	Self-reported smell loss had good discriminative ability to identify abnormal BSIT scores. Moderate associations were found between VAS and BSIT scores (r=0.59)
Qui et al[20]	2020	4	Multi-center case series	394 patients with COVID-19, 60 completed QOD	1) QOD 2) VAS for olfactory/gustatory dysfunction	OD and gustatory dysfunction may be signs of early COVID-19 infection and these symptoms may serve as screening tools
Seo et al[21]	2020	4	Single-center case series	62 patients with mild COVID-19 symptoms, admitted for surveillance	1) QOD-NS 2) 12-Item BSIT 3) Gustatory symptoms: Likert scale 4) Gustatory function: 6-n-propylthiouracail, phenylthiocarbamide, and control strips	QOD and BSIT scores were abnormal, as were measures of gustatory function in this cohort
Desiato et al[15]	2020	3	Prospective cohort	221 adult patients without otolaryngologic symptoms	1) SST 2) QOD-NS 3) Olfactory VAS 4) De Jong Gierveld LS 5) University of California Los Angeles LS	Both olfactory dysfunction and measures of loneliness were common and correlated in a community-based sample of patients

Zou et al[16]	2021	3	Prospective, multi-center cohort from 8 Smell and Taste centers in Germany, Austria and Switzerland	763 adult patients	1) QOD 2) SST 3) VAS for self-assessment	Olfactory-related QOL was associated with SST, age, and self-assessed OD. Patients with post-infectious and post-traumatic OD had worse QOL than those with sinonasal and idiopathic OD.
Erskine et al[23]	2019	4	Qualitative analysis of unstructured written patient accounts from a Smell and Taste Clinic	71 patients who contacted a Smell and Taste Clinic	1) Themes generated by qualitative framework analysis of patient reports	OD has wide-ranging impacts on patients, including in negative emotions, isolation, impaired relationships, and physical health, among other areas.

BDI: Beck Depression Inventory
BSIT: Brief Smell Identification Test
COVID-19: coronavirus disease 2019
CRS: chronic rhinosinusitis
ESS: endoscopic sinus surgery
GAD-7: Generalized Anxiety Disorder
LOT-R: Life Orientation Test
LS: Loneliness Scale
OD: olfactory dysfunction
QOD-NS: Questionnaire of Olfactory Disorder – Negative Statements
QOL: Quality of life
ROC: receiver operating characteristic
SF-8: Short Form Health Survey-8
SF-36: Short Form Health Survey-36
SIT-40: 40-item Smell Identification Test
SNOT-22: 22-item SinoNasal Outcome Test
SST: Sniffin' Sticks Test
SWLS: Satisfaction with Life Scale
TDI: threshold, discrimination, identification
VAS: visual analog scale

Use of a validated measure of QOL in the assessment of patients with OD

Aggregate Grade of Evidence: C (Level 3: 6 studies; Level 4: 1 study)
Benefit: In patients with CRS, using a validated measure of olfactory QOL correlates with quantitative OD at baseline, may potentially serve as a screening tool, and generally associates with improvements in OD after treatment. The utility of an olfactory QOL survey in individuals without sinonasal disease is less clear, but reports suggest there may be value in this approach.
Harm: None anticipated
Cost: Minimal time to complete survey
Benefit-Harm assessment: Benefit for use over non-use of surveys
Value Judgments: The advantage of using an olfactory QOL survey is greater in individuals with known sinonasal disease based on current evidence compared to the healthy population.
Policy level: Use of validated QOL survey is **recommended** in individuals with OD related to CRS.
Use of validated QOL survey is an **option** in individuals with OD without sinonasal disease.
Intervention-A validated olfactory QOL survey should be considered in individuals with CRS and in those who may have other diseases that impact olfaction.

SECTION: VIII. Evaluation and Diagnosis

E. Measurement of cytokine/mucin levels

Olfaction requires odorant molecules to reach the olfactory epithelium, receptor binding, signal transduction and transmission, and interpretation in the central nervous system. Thus, any pathology in this process can result in loss of olfaction, leading to many potential etiologies for olfactory dysfunction. Inflammatory sinonasal disease, such as chronic rhinosinusitis (CRS), is the most common cause of olfactory loss, and it appears that many factors including local inflammation-mediated olfactory epithelium injury, nasal obstruction, and olfactory cleft binding protein and mucous transport abnormalities, among others, may be involved in olfactory dysfunction in CRS.[1] Researchers have attempted to gain greater understanding of the mechanisms involving inflammatory mediators such as cytokines, chemokines and other proteins by assessment of the local microenvironment of the olfactory epithelium.

Lane et al. utilized a mouse model of reversible TNF-α mediated inflammatory infiltration and found thinning of the olfactory epithelium with atrophy of axon bundles in the neural layer, and severely diminished electro-olfactogram responses.[2] TNF-α may also affect olfactory epithelium regeneration, and downstream cytokines may have a role in inflammatory olfactory dysfunction.[3-6] Other murine studies have implicated interleukin (IL)-4, IL-5, IL-13, IL-

17c, chemokine (C-C motif) ligand (CCL)-28, and chemokine (C-C motif) receptor (CCR)-5 in olfactory dysfunction.[7–10]

Six studies of human CRS-related dysosmia have correlated psychophysical olfaction to olfactory epithelium biopsy or olfactory mucus samples.[11–16] Olfaction in CRSsNP was inversely correlated with TNF-α, IL-5 and IL-10, and directly correlated with IL-7 and chemokine (C-X-C motif) ligand (CXCL)-5, while olfaction in CRSwNP was inversely correlated with TNF-α, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, CCL-2, CCL-5, and CCL-11 and directly correlated with IL-6, IL-7, and vascular endothelial growth factor A (VEGF-A).[11,13,15,16] Two other studies utilizing hierarchical cluster analysis and olfactory epithelium tissue biopsies found associations between IL-2, IL-5, IL-13 and CCL-11 and olfaction.[12,14] Only the inverse correlations of IL-5, IL-6, IL-10, IL-13 and CCL-11 to olfaction in CRSwNP were found in multiple studies, with IL-6 also showing a direct correlation in one study.[11,13,15,16]

Four studies have evaluated inflammatory proteins in non-CRS related olfactory dysfunction.[17–20] Schubert et al. found no associations between baseline systemic C-reactive protein, IL-6 and TNF-α to subsequent development of olfactory dysfunction over 10 years and Darnell et al. found a systemic cytokine profile associated with frailty (high IL-1 receptor antagonist, low IL-4, low IL-13) had significantly higher odds of worse olfaction.[17,19] Henkin et al. found that IL-6 levels were significantly higher in the plasma, saliva and nasal mucus of hyposmic patients compared to normosmic patients.[18] Yoo et al. evaluated olfactory cleft mucus concentrations of 18 proteins in non-CRS patients and found inverse correlations between psychophysical olfaction and cyclin-dependent kinase inhibitor 2A (CDKN2A/P16INK4a), basic fibroblast growth factor (bFGF), CCL-2, CCL-20, and granulocyte macrophage colony-stimulating factor (GM-CSF), and a direct correlation with stem cell factor (SCF).[20] Notably, the results from non-CRS studies were largely dissimilar to the findings from the CRS studies, pointing to the likelihood that olfactory dysfunction in CRS-related and non-CRS related etiologies occur via distinct mechanisms.

It must be noted that these human studies described are all observational and thus can only establish associations and are not designed to determine causality. However, these studies do show that the measurement of inflammatory mucus proteins is a viable avenue of

investigation. In summary, numerous nasal mucus proteins have been associated with olfactory function, but only a few cytokines (IL-5, IL-6, IL-10, IL-13 and CCL-11) have shown reproducibility of the associations across multiple studies. This variability is likely due to the heterogeneity of etiology of olfactory dysfunction. Though promising as a way to identify potential therapeutic targets and/or strategies, further investigation is required to transform this potential into a clinical tool.

Table VIII.12. Evidence for measurement of cytokine levels in olfaction

Study	Year	LOE	Study Design	Study groups, Number of subjects	Primary endpoint	Conclusion
Henkin et al[18]	2013	4	Observational (cross sectional)	Control: 9 subjects with normosmia Hyposmia Group: 59 subjects with hyposmia of varying etiology (not CRS) - 12 severe hyposmia - 44 moderate hyposmia - 3 mild hyposmia	Comparison of plasma, urine, salivary and nasal mucus concentrations of IL-6 in hyposmics compared to controls	Overall, IL-6 levels in hyposmic patients significantly higher than controls in plasma, saliva and nasal mucus <u>By etiology:</u> Plasma: all etiologies of hyposmia with significantly higher concentrations of IL-6 compared to controls Urine: Only congenital hyposmia with reduced concentration of IL-6 compared to controls Saliva: Only head injury and burning mouth syndrome etiologies of hyposmia with significantly higher concentration of IL-6 compared to controls

						Nasal mucus: Only post influenza hyposmia and burning mouth syndrome etiologies with significantly higher concentrations of IL-6 compared to controls
Schubert et al[19]	2015	3	Individual Cohort	1,611 subjects from Epidemiology of Hearing Loss Study	Association of serum inflammatory markers (CRP, IL-6 and TNF-α) to SDOIT	No association between serum CRP, IL-6, and TNF-α levels at baseline and subsequent olfactory dysfunction
Schlosser et al[11]	2016	4	Observational (cross sectional)	CRSsNP: 19 subjects CRSwNP: 15 subjects	Correlation of olfactory mucus cytokine concentration to Sniffin' Sticks TDI score	<u>Significant correlations of mucus protein concentration to TDI score</u> - CRSsNP Negative correlation: IL-5 Positive correlation: None - CRSwNP Negative correlation: IL-5 Positive correlation: IL-6, IL-7, VEGF-A
Lavin et al[12]	2017	4	Observational (Cross sectional)	Control: 26 subjects CRSsNP: 37 subjects CRSwNP: 36 subjects	Correlation of eosinophilic cationic protein with charcot leyden crystal protein. CLC protein	Significant strong negative correlation between ECP and CLC protein in all patients. Significant moderate positive correlation

					correlation with IL-5 and CCL11/eotaxin 1. Correlation with CLC protein Sniffin' sticks (threshold only) and UPSIT	between CLC protein and IL-5 and weak positive correlation with CCL11/eotaxin-1 in all patients Significant moderate negative correlation between CLC protein and olfactory threshold and identification in all patients.
Wu et al[13]	2018	4	Observational (Cross sectional)	Control: 12 subjects CRSsNP: 31 subjects CRSwNP: 36 subjects	Correlation of olfactory mucus cytokine concentration to SIT-40	<u>Significant correlations of mucus protein concentration to SIT-40 score</u> - CRSsNP Negative correlation: None Positive correlation: IL-7 - CRSwNP Negative correlation: IL-5, IL-6, IL-10, IL-13 Positive correlation: None
Morse et al[14]	2019	4	Observational (cross sectional)	CRS: 110 subjects	Association of olfactory mucus cytokine concentrations to SIT-40 using cluster analysis and random forest	<u>Univariate regression analysis</u> - Increased concentrations of IL-2, IL-5, and IL-13 significantly associated with

					algorithm to examine cytokines most predictive of SIT score	olfactory dysfunction Multivariate regression analysis - Increased concentration of IL-2 significantly associated with olfactory dysfunction Random forest approach - IL-5 and IL-13 with most predictive of olfactory function in CRS
Yoo et al[20]	2019	4	Observational (Cross sectional)	Non-CRS: 34 subjects Normosmic: 12 Hyposmic/anosmic: 22	Correlation of olfactory mucus cytokine and select protein concentrations to Sniffin' Sticks TDI score	Significant correlations of mucus protein concentration to TDI score - Negative correlation: CDKN2A/p16INK4a, bFGF, CCL2, GM-CSF, CCL20 - Positive correlation: SCF
Soler et al[15]	2020	4	Observational (Cross sectional)	CRSsNP: 25 CRSwNP: 37	Correlation of olfactory mucus cytokine concentration to Sniffin' Sticks TDI score	Significant correlations of mucus protein concentration to TDI score - CRSsNP Negative correlation: None

						Positive correlation: CXCL5 - CRSwNP Negative correlation: CCL2, IL-5, IL-6, IL-13, IL-10, IL-9, TNF-α, CCL5, CCL11 Positive correlation: None
Darnell et al[17]	2020	3	Individual cohort	2084 subjects from the NSHAP	Association of plasma cytokine concentration profiles with olfactory dysfunction measured with the OFFE	Multivariate logistic regression models revealed that only the "frailty" profile (includes high IL-1Ra, low IL-4 and low IL-13) with significantly higher odds of worse identification and threshold testing
Han et al[16]	2020	4	Observational (cross sectional)	CRSsNP: 25 subjects CRSwNP: 46 subjects	Correlation of olfactory mucus cytokine concentration to Sniffin' Sticks TDI score	<u>Significant correlations of mucus protein concentration to TDI score</u> - CRSsNP Negative correlation: TNF-α, IL-10 Positive correlation: None - CRSwNP Negative correlation: IL-4, IL-5 Positive correlation: None

CRS: Chronic rhinosinusitis, CRSsNP: Chronic rhinosinusitis without polyps, CRSwNP: Chronic rhinosinusitis with polyps, SIT-40: 40-item Smell Identification Test, SDOIT: 8-item San Diego Odor Identification test, NSHAP: National Social Life, Health and Aging Project, OFFE: Olfactory function field test (5 item identification + 6 item threshold testing), TDI score: threshold discrimination and identification composite score (score range 1-48), UPSIT: University of Pennsylvania Smell Identification Test, IL: interleukin, CRP: C-reactive protein, CCL: chemokine (C-C motif) ligand, TNF-α: Tumor necrosis factor alpha, CDKN2A/P16INK4a: Cyclin-dependent kinase inhibitor 2A/P16, bFGF: basic fibroblast growth factor, GM-CSF: Granulocyte monocyte-colony stimulating factor, CXCL: chemokine (C-X-C motif) ligand, IFN-γ: interferon gamma

*For psychophysical testing (SIT-40, TDI score, UPSIT, SDOIT and OFFE): higher score indicates better olfactory function

**For correlations: In correlating mucus protein concentrations to psychophysical testing, negative correlation indicates that higher concentrations of protein are associated with lower olfactory function, whereas, positive correlation indicates higher concentrations of protein are associated with better olfactory function

- **Multiple nasal mucus proteins have been associated with olfactory function, with a few cytokines showing reproducibility of association with olfactory function across multiple human and murine studies (IL-5, IL-6, IL-10, IL-13, and CCL-11)**
- **Some of the inconsistency in findings are likely related to the heterogeneity of etiologies of olfactory dysfunction and further study into these associations is required**

  Aggregate Grade of Evidence: C (Majority observational studies with variable results, Level 3: 2 studies; Level 4: 8 studies; Table X-E).

SECTION: VIII. Evaluation and Diagnosis

F. Electro-olfactogram

The Electro-Olfactogram (EOG) is an electrophysiological equivalent of olfactory activation at the level of the olfactory mucosa. It represents the summated generator potentials of olfactory sensory neurons in response to an olfactory stimulus. While this measurement technique has been used extensively in animal research since the 1930s,[1,2] its use in human olfaction research has been limited.

Although pioneering work was performed in the 1960s[3] to 1980s[4], EOG research never arrived in routine clinical assessment probably because of the requirements for sophisticated constant-flow olfactometry,[4] and nasal endoscopy,[5] and the relatively low response yield of approximately 50-70% with high inter-individual variability and low intra-individual variability.[6–9]

Among other results, EOGs have been used to provide evidence for the dominant role of the central nervous system in olfactory desensitization. Specifically, repeated stimulation at short interstimulus intervals produce responses with little or no decrease in amplitude, although simultaneously recorded, EEG-derived olfactory event-related potentials exhibit such a decrease in amplitudes and intensity ratings decrease.[4,10] Leopold et al[11] used EOGs to functionally describe the extent of the olfactory epithelium.[11] They reported the presence of EOG responses and functionally mature olfactory sensory neurons the insertion level of the middle turbinate. Some EOG work also suggested the existence of a specific topographical distribution of olfactory receptors with some recording sites only responding to certain odors,[5] that the EOG was odorant specific[6] (and even specific for odorous enantiomers[12]). Areas that responded maximally to a pleasant odorant were also likely to respond strongly to other pleasant odorants, and a location that responded maximally to an unpleasant odorant was likely to respond strongly to other unpleasant odorants.[7] EOG recordings have also been used to show that peripheral antagonism between odors results in a decrease of odor intensity. Specifically, the odorant bourgeonal (scent of lilies of the valley) is a potent agonist at the human olfactory receptor hOR17-4. Its antagonist undecanal decreases EOG response amplitudes and intensity of bourgeonal following brief exposure to undecanal.[13] In addition, EOG recordings suggested that individuals who perceived big differences across odorants also had big EOG differences across odorants.[7] More recent work utilized EOG responses to demonstrate that psychological conditioning produced significant differences in the peripheral responses between the conditioned and the unconditioned stimulus, demonstrating contextually induced changes at the level of the first neuron in the olfactory system.[14] Similarly, using EOG recordings it was possibly to show that the decreased intensity from retronasally presented odors compared to orthonasal presentation may start at the periphery.[15]

When focusing on the clinical utility of EOG recordings a literature search produced 17 results. After careful reading of abstracts only 3 relevant publications were eligible to be included in the formal analysis (**Table VIII.13**).

On a clinical level EOG recordings were significantly more often obtained in healthy participants than in subjects with olfactory dysfunction suggesting that olfactory disorders are accompanied by a changes at the level of the olfactory mucosa.[16,18] In addition, olfactory training was associated with a significant increase in the number of EOG recordings in response to odors, suggesting improvement in olfactory function with training.[18]

Overall, EOG measurements provide an opportunity to record objective neuronal input from the peripheral olfactory system, while simultaneously obtaining psychophysical responses in awake humans.[19] However, similar to other measures of chemosensory activation at the nasal mucosa,[20,21] the evidence level of EOG-related studies in a clinical context is currently low.

Table VIII.13. Diagnostic use of the Electro-Olfactogram

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Furukawa et al[16]	1989	4	Observational study	1- subjects with olfactory loss (n=34)	Presence of EOG response	1 - Subjects with ”peripheral“ cause of olfactory loss have less responses than those with “central” loss. 2 - The number of EOG responses increases with increasing olfactory function.
Turetsky et al[17]	2009	3	Observational study	1 - subjects with schizophrenia (n=21) 2 - healthy controls (n=18))	EOG amplitude	1 - Larger EOG amplitudes in schizophrenic subjects compared to controls

Hummel et al[18]	2018	3	Observational study	1 - subjects with idiopathic and post-infectious olfactory loss (n=38) 2 - healthy controls (n=27)	presence of EOG response	1 - Subjects with olfactory loss have less EOG responses than controls. 2 - Normosmic subjects have more EOG responses than hyp- or anosmic participants. 3 - Following olfactory training in patients the number of EOG responses increased.

- **More investigation is necessary to determine if use of EOG in routine clinical practice would give additional useful clinical data, as well as to determine how an EOG could be more easily utilized in routine clinical practice.**

Aggregate Grade of Evidence: C (Level 3 studies: 2; Level 4 studies: 1)

SECTION: VIII. Evaluation and Diagnosis

F. Role of bloodwork/lab values

The literature on laboratory studies for evaluation and diagnosis of olfactory dysfunction is quite sparse. This is likely why many previous position papers, such as the 2017 Position Paper on Olfactory Dysfunction,[1] do not cover this topic. In the absence of systematic reviews and high-level evidence, lower-evidence reports and reasoning from first principles help to relate certain blood tests and laboratory studies to conditions which are associated with olfactory dysfunction.

Derin et al[2] shed light on the role of vitamin B12 in olfactory dysfunction. In a case control study they showed that in the vitamin B12-deficient group, hyposmia and anosmia were evident in 56.4% and 5.1% of the patients, respectively, but no subjects in the control group had olfactory dysfunction, suggesting a possible role for vitamin B12 blood testing in patients with hyposmia/anosmia (**Table VIII.14**). Vitamin B1 (thiamine) deficiency has also been implicated in olfactory dysfunction,[3] but no formal study has assessed the role of vitamin B1 blood testing for the evaluation and diagnosis of anosmia. The evidence-base for zinc deficiency as a cause for smell and taste dysfunction is also sparse.[4,5] Moreover, zinc nutritional status is difficult to

measure adequately using laboratory tests.[6] Present recommendations do not consider the numerous dietary factors that influence the bioavailability of zinc and copper, and the likelihood of toxicity from zinc supplements. The current assumed range between safe and unsafe nutritional intake of zinc is relatively narrow,[7] bearing in mind anosmia has been associated with the use of zinc-containing nasal gels or sprays, leading to a warning by the FDA in June 2009. These products have since been taken off the market.[8]

Both hypogonadotropic hypogonadism, i.e. Kallmann syndrome, and Klinefelter syndrome are associated with anosmia. Kallmann syndrome occurs more often in males than in females, with an estimated prevalence of 1 in 30,000 males and 1 in 120,000 females, and is associated with microphallus, cryptorchidism/small testes, delayed puberty and delayed bone maturation. In their study Dissaneevate et al. showed that fifty-six percent had a family history of either anosmia or infertility.[9] Laboratory diagnosis is based on a constellation of low serum levels of testosterone, LH and FS.[9–12] This hormone profile rules out a primary testicular disorder. However, before diagnosing congenital hypogonadotropic hypogonadism, it is important to rule out a pituitary tumor (by imaging studies), juvenile hemochromatosis, or any systemic condition, affecting gonadotropin secretion and pubertal development.[10] With genetic testing becoming more readily available, this will also be an avenue of laboratory investigation, carried out by specialist services.

Various neurologic conditions can present with loss of sense of smell, such as Parkinson's and Alzheimer's disease[13]. Although no blood tests exist for Parkinson's disease at present, a promising blood test for Alzheimer's disease has been developed recently.[14] Thinking of other causes of olfactory dysfunction, e.g. toxins, such as heavy metals or lead,[15] Sjogren's syndrome,[16] Diabetes,[17] Wilson's disease,[18] liver cirrhosis,[19] etc., clinical suspicion needs to guide the physician on which test(s) to order or whether to refer the patient to a colleague with expertise in a specific underlying etiology.

Recently there has been an abundance of literature assessing symptoms of anosmia and dysgeusia due to COVID-19, with testing being indicated for hyposmia/anosmia and suspected COVID-19 infection. It is clear and in accordance with guidance from world and national public health organizations that COVID-19 testing is indicated in sudden-onset anosmia, as outlined in

numerous studies.[20–22] More importantly, COVID-19 represents one of the only causes of post-viral olfactory loss (PVOL) for which antibody testing could become a standard of care as part of the diagnostic work-up, taking into account preliminary data obtained so far.[23,24]

In summary, evidence-based literature on laboratory studies for evaluation and diagnosis of olfactory dysfunction is very sparse and no firm recommendations can be made at this stage. Further research is required to assess whether a panel of laboratory tests in a large number of patients with hyposmia/anosmia would be useful for routine evaluation and diagnosis of olfactory dysfunction. Until then, thorough history-taking, review of systems and knowledge of the various causes of olfactory dysfunction, are still required to guide the physician on a case-by-case basis.

Table VIII.14 Role of bloodwork in routine workup of olfactory dysfunction

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Derin *et al*.	2016	3	Retrospective case control study	1) Thirty-nine patients with low vitamin B12 levels 2) 34 controls	Threshold discrimination identification scores on psychophysical testing (Sniffin' Sticks) of olfactory function	'Olfactory dysfunction may be present in patients with vitamin B12 deficiency'. Negative correlation of age with odor identification score

- **Ordering laboratory testing for the OD patient is better based on specific history as opposed to sending routine tests on all patients.**

Aggregate Grade of Evidence: C (Level 3: 1 study), see other sections under Etiology for other specific potential laboratory investigations suggested based on specific history.

SECTION: VIII. Evaluation and Diagnosis

G. Specific evaluation and workup for phantosmia

Phantosmia is a qualitative olfactory disorder in which a person perceives an odor in the absence of an odorant stimulus.[1] As with other olfactory disorders, a thorough history is required to make the diagnosis. Having an understanding of the typical presentation and progression can allow medical providers to elicit specific details from the patient history if phantosmia is suspected.

Similar to migraine, phantosmia occurs most frequently in females starting in the second or third decade of life. Initial episodes often begin sporadically without an identifiable inciting event, prompting the person to seek an external source for the unusual odor. Episodes occur more frequently and for longer duration as time goes on, eventually occurring on a daily basis and lasting for most of the day.[1,2] Patients will often describe phantom smells as smoky, burned, foul, unpleasant, spoiled or rotten. [1–3] Phantosmia can occur in one or both nostrils. Occlusion of the affected nostril(s), intranasal instrumentation, Valsalva, head inversion, forced crying, gagging, and sleep are some reported activities that can abort the phantom smell; however, with time, these methods eventually become ineffective.[1–5]

In contrast to other qualitative olfactory disorders, most cases of phantosmia are idiopathic and less commonly present after upper respiratory infection (URI), head injury or with aging.[1,5,6] There are several neurologic and psychiatric disorders that have been shown to be associated with phantom smells including temporal lobe epilepsy, migraine disorder, Parkinson disease, intracranial neoplasm, depression, schizophrenia, and olfactory reference syndrome. Other reported associations include chronic rhinosinusitis, iatrogenic causes, and metabolic disorders.[1,3,5,7–14] The exact mechanism is unknown with each of these potential etiologies but both peripheral and central triggers have been hypothesized.[1,2,4,7,13,15] Certainly, olfactory processing in the central nervous system is a major factor. Given the wide range of possible causes, performing a complete history and review of systems can help elucidate a possible etiology and therefore guide treatment more effectively.

A standard head and neck examination is indicated for all patients with suspected phantosmia. Examination should include bilateral nasal endoscopy to assess the patency of the olfactory cleft, rule out the presence of polyps, tumors or sinonasal mucosal edema, as well as any postoperative changes, adhesions or crusting if applicable. For additional confirmation, each nostril should be blocked individually to note the effect on the phantom smell. If the trigger or cause of the phantom odor is related to the peripheral olfactory neurons, anesthetizing the olfactory area should abort the phantom smell and can help determine if it is unilateral or bilateral.[1,2,16,17] A basic neurologic examination should be performed in addition to assessing the patient's overall demeanor during history of physical examination given the association with several neurologic and psychiatric disorders.[8,16,17]

Although phantosmia has been shown to be associated with a decrease in quantitative olfactory function in the affected nostril(s), this is not always the case.[5,7,8] Nevertheless, uninasal olfactory testing (identification and possibly threshold testing) should be performed to document the patient's baseline olfactory function at initial evaluation.[1,2,8,16,17]

Imaging should include a computed tomography (CT) scan of the head/sinuses and/or magnetic resonance imaging (MRI) of the brain to rule out intracranial or sinonasal pathology.[1,2,16,17] Electroencephalography (EEG), positron emission tomography (PET) and functional MRI (fMRI) are generally reserved for research purposes and not recommended for the initial workup of phantosmia.[2,17] Laboratory studies are not needed in the workup of phantosmia. Appropriate referrals to neurology, psychiatry, endocrinology, etc., for further evaluation and/or treatment should be considered.

SECTION: IX. Management

A. Prognosis and Spontaneous Recovery

Estimating true spontaneous recovery time after the onset of olfactory dysfunction (OD) is difficult, as many patients delay reporting smell loss. This makes it difficult to establish an etiology, confirm the duration, and assess other characteristics of the loss. Olfactory recovery times may be dependent on the disease that caused the loss of smell. However, only a handful

of diseases have been studied in isolation for humans, and follow-up times vary widely across studies leading to many discrepancies in recovery data. For instance, removing studies with subjective measures,[1–3] smell loss from head injury is related to slower and lower recovery rates (0 - 44 %) than post-viral loss (0 - 77 %).[4–13] Additionally, medical, surgical, and alternative interventions may change the recovery times of smell loss. Without minor interventions, smell may spontaneously recover from diseases that result in nasal congestion or acute inflammation (with minimal damage to the olfactory epithelium) as these symptom resolve.[7,8,11,14,15] Interestingly, COVID-19, a disease that attacks the underlying structure or supporting cells[16] rather than the sensory neurons of the olfactory epithelium, may show recovery within weeks after symptoms have resolved, but we are now seeing regression of symptoms, with the addition of significant parosmias presenting months later.[17–20] Olfactory sensory neurons do not express the necessary viral entry gene Angiotensin I Converting Enzyme 2 (ACE2) for COVID-19 infection, unlike supporting cells underlying the olfactory epithelium (e.g., sustentacular or microvillar cells). These cells manage epithelial maintenance through delivery of glucose to olfactory sensory neurons (OSNs) and local salt/water balance. It may be that only when it comes time for the inherent regenerative process to take place within the neuroepithelium, is when we see the true effect of the damage to these sustentacular cells. However, diseases that cause direct damage to the olfactory epithelium (either supporting structure, sensory neurons, or both) may require complete neurogenesis for even primary recovery. Within 30 days, several young, mature neurons are grown in the epithelium (via horizontal basal cells) while another 30 to 60 days are needed for the olfactory epithelium to reacquire a population of neurons similar to a healthy state.[21] Many individuals with a sensorineural loss show recovery between this time and the first year from loss. While an increased duration of loss has been associated with worse recovery in multiple studies,[8–10,12,22] others showed no effect with duration of loss.[5,7,23] After 3 years of loss, the chance of any recovery is severely reduced, yet, there are cases in which individuals have recovered even up to 9 years after a traumatic incident.[2,3,24] However, even after recovery, a portion of patients will still experience parosmia or a distorted sense of smell[11,25,26,27] and phantosmia[28], presumably due to altered ORNs and their retargeting of glomeruli in the OB or onward at the level of the cortex.[21,29,30]

Several other factors may affect the natural course of neurogenesis impacting recovery times for smell loss. In general, there is a negative correlation between age and recovery, in that losing smell at an older age results in slower recovery across multiple studies.[7,8,10,12,23] However, a lack of correlation has also been reported.[9,22,31,32] Decreased recovery may be due to a reduced regenerative capacity of OSNs that comes with advancing age.[33] In parallel, the size of the olfactory epithelium decreases with age and there may be more respiratory metaplasia over years of insult from diseases in which the damaged olfactory epithelium is replaced by respiratory epithelium and no longer functions as a sensory organ.[33,34] This can be seen in mice in which telomere shortening (a basic mechanism of cellular aging) impairs olfactory epithelium regeneration, but not homeostatic conditions.[35] Similarly, the decrease of afferent synaptic input into the brain, decreased neural response, and breakdown of synaptic connectivity and thus limited plasticity with age in the olfactory bulb and other important processing areas, may lead to less efficient central recovery.[33,34,36] There may also be a gender influence, with some reports showing females recovering more often than males[5,7–9]; however, again, many reports have shown no difference.[10,12,22,23,32] (Table IX.1) Lastly, although most studies show no link between parosmia at initial diagnosis and better olfactory recovery,[7] this has been postulated as a potential predictive sign.[11]

Table IX.1 Prognosis and Spontaneous Recovery

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Sumner[2]	1964	4	Case-series (within a year; 2 to 16 years)	1) 1,167 patients 2) 101 PTOD (series)	Δsubjective: unknown	39 % of PTOD recovered at varied time, but typically within 10 weeks except with rare cases (5 years for one).
Zusho[3]	1982	4*	Retrospective Cohort	1) 56 PTOD	Δsubjective: unknown	14% of PTOD recovered at varied times (case study with 7 years).

			(Across 15 years)			
Deems et al[4]	1991	4*	Retrospective Cohort (5 months to 6 years)	1) 306 OD patients	1) ΔUPSIT	No recovery for PTOD and PVOD patients, but some recovery for rhinosinisutus (RS). No percentages given.
Doty et al[5]	1997	4	Case-series (1 months to 13 years)	1) 248 PTOD 2) 66 PTOD (series)	1) ΔUPSIT 2) Δquestionaire	36 % showed improvement, but this, along with duration, was not significant. Chane with age modeled, but not reported.
Mori et al[9]	1998	4*	Retrospective Cohort (2 month to unknown)	1) 889 OD patients	1) ΔT&T	Improvement by etiology (AR>RS>PVOD>PTOD). Longer duration of disorder and sex (male) lead worse prognosis in PTOD and RS, but not PVOD. No effect of age on prognosis.
Hummel et al[15]	1998	2	Randomized-Controlled Trial (0, 2, 4, 6, and 35 days)	1) 12 AR control 2) 12 AR w/ Oxymetazoline (0.25 mg/mL) 2) 12 AR w/ Oxymetazoline (0.5 mg/mL)	1) Δsubjective sypmtoms 2) ΔTDI 3) Δrhinometry 4) ΔcsERPs	Within a month, olfactory outcomes increased from day 0 to 35. Congestion dependency was found in some, but not all, outcomes.
Reden et al[12]	2006	3	Retrospective Cohort (1 to 216 months)	1) 262 PVOD 2) 99 PTOD	1) ΔTDI	32% of PVOD and 10% of PTOD improved in olfactory. Age was negatively associated with improvement.

Reden et al[11]	2007	4*	Retrospective Cohort (no range given; mean 11 months)	1) 392 OD patients	1) ΔTDI	Improvement by etiology (RS/AR (31%)>PVOD (27%)>PTOD/Idiopathic (18%)). PVOD had more parosmia, but this did not impact recovery.
London et al[8]	2008	3	Retrospective Cohort (3 to 283 months)	1) 542 OD patients	1) ΔUPSIT	Among all patients, sex (female), age, and duration of impairment impacted recovery. Among patients with OD at initial assessment, etiology (RS/AR (49%)>PVOD (48%)>PTOD(44%)>Idiopathic(34%)) impacted recovery.
Mueller and Hummel[24]	2009	5*	Case-report	1) 1 PTOD	1) TDI 2) csERPs	Patient recovers after 9 years of subjective loss
Rombaux et al[32]	2010	4	Case-series (4 to 18 months)	1) 27 PVOD patients	1) ΔTDI 2) ΔcsERPs 3) Δretronasal ID	26% of patients improved and csERPs had some predictive value (44% sensitivity, 83% specificity). Age and sex did not affect recovery.
Hummel and Lötsch[7]	2010	4*	Retrospective Cohort (1 to 106 months)	1) 463 PVOD 2) 220 AR/RS 3) 211 PTOD	1) ΔTDI	Improvement by etiology (RS/AR (76%) > PVOD (46%) > PTOD (44%)). Lower age, increased parosmia, and sex (female) had increased recovery rates.

Rombaux et al[13]	2012	4	Case-series (no range; mean 14.6 months)	1) 28 PVOD 2) 32 PTOD	1) ΔTDI 2) ΔOB volume 3) Δretronasal ID	36% of PVOD and 25% of PTOD improved in olfactory. Larger bulbs related to better recovery.
Lee et al[1]	2014	4	Case-series (mean 33 months)	1) 63 PVOD 2) 20 Control	1) Δsubjective: VAS, Binary 2) ΔBTT (N = 25)	86% reported subjective improvement and unknown for threshold testing.
Brann and Firestein[36]	2014	1	Review	N/A	N/A	Mechansims underlying neurogenesis in the subgranular zone, the subventiricular zone, and olfactory epithelium
Mobley et al[33]	2014	1	Review	N/A	N/A	Mechanisms underlying olfactory neurogenesis with age.
Doty[34]	2014	1	Review	N/A	N/A	Age-related declines in olfactory ability along with regeneration decreases.
Fan et al[31]	2015	3	Retrospective Cohort (1 - 52 months)	1) 107 PTOD	1) ΔUPSIT	16.8% recovered and no prognosis factors were relevant to recovery
Konstantinidis et al[22]	2016	2	Randomized-Controlled Trial (0, 8, 16, 25, 32, 40, 48, 56 weeks)	1) 41 PVOD patients 2) 36 short Olfactory Training 2) 34 long Olfactory Training	1) ΔTDI	37% of PVOD control improved. For control, duration of olfactory loss, but not age or sex were related to improvement.

Schwob et al[21]	2017	1	Review	N/A	N/A	Horizontal Basal Cell (HBC) contributes to OE damage and mechanisms are discussed
Hummel et al[37]	2017	1	Review	N/A	N/A	List of interventions that have an impact on olfactory loss recovery
Pellegrino et al[14]	2017	3	Prospective Cohort (21 - 90 days)	1) 57 RS 2) Control	1) ΔTDI 2) Δretronasal ID 3) Δrhinometry	Smell (and nasal dimensions) decreased during RS, but almost all patients improved upon recovery. No imporovement in retronsasal smell.
Cavazzana et al[23]	2018	4*	Retrospective Cohort (mean 1.94 years)	1) 791 post-viral patients	1) ΔTDI	Age and severity were important prognostic factors.
Ogawa et al[10]	2020	2*	Retrospective Cohort (0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 36, 39, 42 months)	1) 82 PVOD	1) ΔT&T	77% of patients showed recovery with 60% recovering within six months. Lower age and more residual function, but not sex, lead to higher recovery rates.

TDI represents the composite score for the Sniffin' Sticks, comprised of three subtests: threshold (T), discrimination (D) and Identification (I)

Post-Traumatic Olfactory Disorder (PTOD), Post-Viral Olfactory Disorder (PVOD), Allergic Rhinitis (AR), and Rhinosinusitis (RS)

UPSIT represents the 40-items University of Pennsylvania Smell Identification Test

Δ represents a change between end-points

T&T represents a olfactometory test of threshold (Zusho 1983)

BTT represents butonal-threshold testing

*Ranked down a level of evidence due to methodological concerns

Recovery rates with limited intervention vary widely based on underlying etiology, age and duration of loss prior to any definitive intervention.

Aggregate Grade of Evidence: C (Level 2: 3 studies; Level 3: 3 studies; Level 4: 11 studies; Level 5: 1 study)

Benefit: Earlier intervention after OD may potentially speed up recovery. Elderly and PTOD are associated with slower and poorer recovery and therefore may benefit most.

Harm: None anticipated

Cost: Monetized value for any relevant intervention and follow-up appointments as needed to track recovery

Benefits-Harm assessment: There is a potential benefit for follow-up appointments with intervention over natural recovery without follow-up

Value Judgments-It is difficult to conduct well-controlled longitudinal studies to measure olfactory recovery rates as this relies on clinical evaluation in a timely manner and continuous contact during follow-up investigations. Accurate reporting of onset and recovery rates may enable early intervention while providing data regarding effects of etiology and various demographics on recovery. Additionally, clinicians/researchers should avoid patient populations heterogeneous in respects to etiology and medical, surgical, and alternative interventions when studying recovery from olfactory disorders.

Policy level: Follow-up investigation is **recommended** in individuals with OD.
Early intervention strategies to mitigate chronic OD is **recommended**.

Intervention: There is a need for well-designed studies examining the spontaneous course of resolution in patients with OD, and there is evidence that intervening early for patients with loss of smell is helpful for accelerating recovery. Research protocols for therapeutics should balance the restriction of patients most likely to recover to avoid confounding results (e.g restrict to at least 6 months loss) versus the likelihood of being able to help more patients early in the time course of loss and seeing a treatment effect (e.g. restrict to loss no longer than one year).

SECTION: XI. Management
B. Treatment of post-traumatic loss

While spontaneous recovery has been observed following some cases of post-traumatic olfactory loss,[1] several studies have investigated treatment with medications. One study reported that spontaneous improvement rate was only 10% on average after 23 months of observation.[2] Kampo medicines (Japanese herbal medicine), zinc or vitamin preparations, topical or systemic steroids, and adenosine triphosphate have been used to treat post-traumatic olfactory dysfunction. Some recent reports indicate that olfactory training is also effective in recovering olfactory function.[3]

From Kampo medicine, tokishakuyakusan treatment improved olfactory function in 42% of patients with post-traumatic olfactory dysfunction.[4] In another study, 7 patients with post-traumatic olfactory dysfunction were treated with kamikihito. In this study, 1 patient recovered, 5 patients improved, and 1 patient showed no change.[5]

For zinc, although a prior double-blind cross-over study of 106 patients found no statistically significant effects on either taste or smell after 3-4 months of treatment,[6] a recent prospective randomized study compared the efficacy of four treatments: zinc gluconate, prednisolone, zinc with prednisolone and no medication in 145 patients with traumatic anosmia and concluded that zinc gluconate has a promising effect for treating traumatic anosmia.[7] In another study, 95 patients with post-traumatic olfactory dysfunction were treated with either zinc sulfate only, combination of zinc sulfate and the "usual" therapy (topical corticosteroids and systemic vitamin B complex), or the usual therapy. Patients who were administered zinc sulfate demonstrated significantly higher improvement rates than those who received the usual therapy.[8] Another study reported that 22 patients with post-traumatic olfactory dysfunction were treated with zinc sulfate, tokishakuyakusan, and vitamin B_{12} complex, and 5 patients were cured, 5 patients improved, 10 patients showed no change, and 2 patients showed an exacerbation of symptoms.[9]

For steroids, some case studies have reported the efficacy of topical or systemic steroids. A total of 108 patients with post-traumatic olfactory dysfunction were treated with topical steroids, and the improvement rate was 25%.[10] In another study, 12 patients with post-traumatic

olfactory dysfunction were treated with topical betamethasone, with only 1 out of 12 patients showing an improvement in the olfactory test score. Five patients were also treated with topical dexamethasone, and 3 out of the 5 patients showed an improvement.[11]. In another study, 116 patients with post-traumatic olfactory dysfunction were treated with systemic prednisolone (60 mg/day for 3 days, tapered every 3 days for 15 days), and the olfactory threshold improved in 19 patients.[12] Patients with post-traumatic olfactory dysfunction were treated with topical betamethasone and the improvement rate was 29%. In this report, the improvement rate between patients who were administered steroids and those administered tokishakuyakusan was compared, but no significant differences were observed.[4]

For vitamin A, in a double-blinded, placebo-controlled study, vitamin A at a dose of 10,000 IU per day was administered to 52 patients with olfactory loss, including 19 patients with post-traumatic olfactory loss, for 3 months. No significant improvement (as evaluated by the Sniffin' Sticks olfactory test) was observed 5 months after the initial test.[13]

For olfactory training, a prospective study with 38 patients with post-traumatic olfactory dysfunction was performed to investigate the effect of olfactory training.[3] The training group underwent olfactory training for 5 min twice daily using the following four odorants: phenylethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves). Compared to the control group, the training group had significantly higher olfactory function scores, as measured by the Sniffin' Sticks test at 16 weeks. The improvement rates of both groups were 33% and 13%, respectively. In another study 16 of 52 patients responded to olfactory training. The authors found factors including the absence of a cribriform plate fracture, absence of olfactory bulb encephalomalacia or siderosis, deep olfactory fossa (>4.9 mm) and larger olfactory bulb volumes (>27.1 mm^3) were related to a better prognosis.[14] Olfactory training has also been reported to be more effective in improving olfactory threshold scores in anosmic patients and in improving identification scores in hyposmic patients.[15]

In conclusion, no randomized controlled trials have been performed evaluating any of these interventions on only a post-traumatic olfactory loss group. In order to fully investigate the efficacy of a medication or other intervention, it is necessary to conduct randomized-controlled trials and evaluate therapeutic interventions at an early stage after injury. With the existing data,

olfactory training could potentially be helpful for these patients, with more data needed before definitive conclusions can be made regarding use of steroids, oral zinc or Kampo medicine. In addition, due to the limited efficacy of treatment options for post-traumatic olfactory dysfunction, patient counseling about hazardous events and safety issues is helpful since persistent olfactory dysfunction results in a higher level of disability and lower quality of life.[16]

Table IX.2. Section Evidence Summary: Management of Post-Traumatic OD

Study	Year	LOE	Design	Study groups	Clinical endpoints	Conclusion
Reden	2006	4	Retrospective	n = 99 Post-traumatic olfactory dysfunction Observation	Outcomes 10% improved, 83% no change 7% worsen measured by Sniffing' Sticks	Spontaneous improvement rate of post-traumatic olfactory loss was poor.
Konstantinidis	2013	3	Prospective	n = 38 Post-traumatic olfactory dysfunction 23/38 Olfactory training patients for 16 weeks 15/38 Control patients	Outcomes 33% of training patients 13% of controls improved measured by Sniffing' Sticks	Olfactory training is useful for treatment of post-traumatic olfactory dysfunction.
Miwa	2005	4	Retrospective	Post-traumatic olfactory dysfunction Tokishakuyakusan vs. Topical steroids	Outcomes 41.7% improved by Tokishakuyakusan 28.8% by Kamikihito measured by T&T olfactometry	No significant difference in improvement rates between tokishakuyakusan and topical steroids was observed.
Shiga	2014	4	Retrospective	n = 13 Post-traumatic olfactory dysfunction 6/13 Tokishakuyakusan 7/13 Kamikihito	Outcomes 2/6 (33%) improved by Tokishakuyakusan 6/7 (86%) by Kamikihito measured by T&T olfactometry	Kamikihito is useful for treatment of post-traumatic dysfunction
Jiang	2015	2	Prospective	n = 145 Post-traumatic olfactory dysfunction	Outcomes 11/39 (28%) improved by Zinc gluconate and prednisolone	Zinc gluconate has a promising effect in treating post-traumatic anosmia.

				39/145 Zinc gluconate for month and prednisolone for 2weeks 35/145 Zinc gluconate only 34/145 Prednisolone only 37/145 No medication	9/35 (26%) Zinc gluconate only 4/34 (12%) Prednisolone only 1/37 (3%) No medication measured by phenyl ethyl alcohol (PEA) odor detection threshold test	
Aiba	1998	4	Retrospective	n = 95 Post-traumatic olfactory dysfunction 4/95 Zinc sulfate 300mg/day 70/95 Topical corticosteroids and systemic vitamin B complex 21/95 Zinc sulfate and the complex	Outcomes 2/4 (50%) improved by zinc sulfate 11/70 (43%) by steroids and systemic vitamin B complex 9/21 (16%) by zinc sulfate and the complex measured by patients' self-reported scores	Zinc sulfate is significantly more efficacious than steroids and systemic vitamin B complex against post-traumatic olfactory dysfunction.
Kitano	2013	4	Retrospective	n = 57 Post-traumatic olfactory dysfunction	Outcomes 45% of improvement rate Prognosticator T&T olfactometry and intravenous olfactory test (Alinamin test) results	Positive responders on olfactory tests at the first visit get better recovery of olfactory function than non-responders.
Mori	1998	4	Retrospective	n = 108 Post-traumatic olfactory dysfunction Topical corticosteroids	Outcomes 25% of improvement rate by patients' self-reported scores	Post-traumatic olfactory dysfunction treated with topical steroids has poor recovery and prognosis.
Ikeda	1995	4	Retrospective	n = 17 Post-traumatic olfactory dysfunction 12/17 Topical nasal drop of 0.1% betamethasone	Outcomes 1/12 (8%) improved by topical betamethasone 3/5 (60%) improved by oral prednisolone	Corticosteroids may induce regeneration of olfactory receptor cell axons and reestablishment of contact with cells in the olfactory bulb.

				5/12 Oral administration of prednisolone		
Jiang	2010	4	Retrospective	n = 116 Post-traumatic olfactory dysfunction Oral prednisolone (60 mg/day for 3 days, tapered every 3 days for 15 days)	Outcomes 16% improved by oral steroids measured by PEA odor detection threshold test	Oral steroid administration is efficacious in limited patients with post-traumatic dysfunction.
Reden	2012	1	Prospective	n = 19 Post-traumatic olfactory dysfunction 10/19 Vitamin A 10,000 IU per day oral administration for 3 months 9/19 placebo controls	Outcomes No significant improvement evaluated by Sniffin' Sticks test.	Vitamin A is not useful in the treatment of post-traumatic olfactory dysfunction.
Altundag	2021	4	Retrospective	n = 52 Post-traumatic olfactory dysfunction Olfactory training	Outcomes 16/52 (31%) responders to olfactory training 36/52 (69%) non-responders	Good prognosticators were no cribriform plate fracture, no olfactory bulb encephalomalacia, no siderosis, deep olfactory fossa and large olfactory bulb volume.
Pellegrino	2019		Prospective	n = 42 Post-traumatic olfactory dysfunction 18/42 hyposmia 24/42 anosmia	Outcomes Greater threshold improvement in anosmic patients Better identification ability in hyposmic patients Evaluated by Sniffin' Sticks test	Olfactory training is effective to both anosmia and hyposmia.

Treatment of Post-Traumatic Olfactory Dsyfunction

Aggregate Grade of Evidence: C (Level 1: 1 study; Level 2: 2 studies; Level 3: 1 study; Level 4: 9 studies)

Benefit: Olfactory training may be efficacious in limited patients with post-traumatic dysfunction. Oral steroids, Kampo, oral zinc medications may also benefit these patients,

although the data is not as robust to support this.
Harm: High dose steroids may induce systemic adverse effects. Some Kampo medications can elevate LFTs.
Cost: Expense for comparatively prolonged use of medication to restore olfactory function. Olfactory training is very inexpensive.
Benefits-Harm assessment: Beneficial to less than half of patients with post-traumatic olfactory dysfunction with little side effects
Value Judgments: It is worth trying treatment for post-traumatic olfactory dysfunction at an early stage after injury.
Policy level: Use of olfactory training is **recommended** in patients with post-traumatic olfactory dysfunction.
Use of oral steroids, Kampo and zinc medications are **options** in patients with post-traumatic olfactory dysfunction.
Intervention: Olfactory training should be considered in patients with post-traumatic olfactory dysfunction.

SECTION: XI. Management

C. Treatment of underlying sinonasal inflammatory etiologies

1. Medical treatment for CRS or AR-related olfactory loss

Olfactory dysfunction (OD) affects a significant portion of the general population with some reports estimating it to be as high as 24%.[1] Inflammatory nasal pathologies such as chronic rhinosinusitis (CRS) and allergic rhinitis (AR) are the most common forms of acquired OD, particularly in younger populations worldwide.[2] Smell loss in CRS is likely caused by a combination of factors that either inhibits odorant transport to the olfactory cleft and/or odorant transduction at the level of the olfactory neuroepithelium. These inflammatory changes may also lead to degeneration of the olfactory epithelium, further causing a reduction in smell.[3] Similar inflammatory pathophysiology is thought to contribute to OD in AR, but the degree of OD in AR is less severe and specific mechanisms are likely to differ.[4] Therapies for OD in CRS/AR aim to decrease the regional sinonasal inflammatory burden and therefore mimic those used to treat CRS and AR in general. It is important to keep in mind that the focus of this section is to review evidence associated with medical treatment of OD specifically; therefore, evidence and recommendations will be provided specific to olfaction and agnostic to any possible non-olfactory benefits that these medications may confer in CRS and AR patients.

The majority of clinical studies investigating olfactory outcomes include subjective assessments and/or olfactory psychophysical tests. Subjective assessments include measures such as olfaction specific-visual analogue scales (VAS), subjective symptom scores, and quality of life questionnaires (e.g. Questionnaire of Olfactory Dysfunction (QOD)). Objective olfactory psychophysical tests may include forced-choice identification, smell discrimination, and olfactory thresholds. Commonly employed psychophysical tests include, but are not limited to the University of Pennsylvania Smell Identification Test (UPSIT), Sniffin' Sticks (SS) Test, Barcelona Smell Test (BAST), and Butanol Threshold Test (BTT).[5] As evident in the accompanying tables, the treatment of OD in chronic sinusitis with nasal polyps (CRSwNP) has been studied to a greater degree compared to chronic rhinosinusitis without nasal polyps (CRSsNP) or in AR. This is likely secondary to the greater severity and higher prevalence of OD in CRSwNP.[6]

In CRSwNP, there is grade A evidence comprised of randomized controlled trials demonstrating that oral steroids and some biologics improve subjective and psychophysical metrics of olfactory dysfunction.[7–11] Topical steroids also appear to improve olfactory function based on grade A evidence, but most studies demonstrate a benefit in subjective metrics only and more studies looking at psychophysical metrics are needed. Dupilumab and omalizumab have been studied in severe CRSwNP patients and, based on grade A evidence that includes studies assessing subjective and psychophysical metrics, these medications are recommended for OD related to severe CRSwNP after failure of other medical and surgical treatment options, as part of a patient-centered shared decision making process. There is limited grade B evidence for mepolizumab, with available evidence demonstrating benefit in subjective measures of OD only.[12]. Oral antibiotics and antileukotriene therapy have been studied with randomized controlled trials, but they do not appear to provide clear benefit in regards to olfaction which therefore precludes their routine use specifically for OD in CRSwNP. In patients with CRSwNP due to aspirin-related respiratory disease (AERD), aspirin (ASA) desensitization and daily ASA therapy may be considered, particularly as an option following sinus surgery. There are few randomized controlled clinical trials investigating ASA use and the benefit on olfaction is unclear with mixed study results. Further studies are needed.

Topical steroids are the mainstay of medical treatment of OD in CRSwNP and should be used as maintenance therapy in light of their minimal side effect profiles. Benefits have been noted as early as after 1 week of regular use. Oral steroids may be recommended, but should be administered infrequently and for short durations due to systemic side effects. Studied duration of oral steroid treatment in CRSwNP ranges from 1-2 weeks with evidence suggesting that there is an initial benefit with return to baseline symptoms within 3 months following treatment.[13] For biologics, available evidence suggests that subjective and psychophysical scores decline as early as 8 weeks after cessation of thearpy.[8] Assessing the comparative effectiveness of topical steroids, oral steroids, and biologics is challenging due to the variable patient populations enrolled in clinical trials and frequent use of combination therapy with topical intranasal steroids being used as a maintenance medication in the majority of studies. In CRSsNP, data on treatment of OD is more limited and no clear benefit has been demonstrated in a randomized manner. Topical steroids and oral steroids are potential treatment options, and the decision to treat OD with these medications should be individualized. Data on macrolide therapy is limited and the available literature is conflicting.[14–17] Therefore, no recommendation can be made regarding macrolide therapy for OD in CRSsNP refractory to more conservative therapy.

In AR, there are few randomized controlled clinical trials investigating olfactory outcomes. Topical intranasal steroids are recommended for treatment of OD in AR, with some randomized clinical trials demonstrating benefit in objective and subjective assessments of olfaction.[18–23] The literature on immunotherapy primarily consists of case series and one RCT which together demonstrate improvement in subjective and objective olfactory outcomes.[24–28] Therefore, immunotherapy may be considered a treatment option. Available randomized clinical trials have demonstrated no clear benefit of antihistamines over topical nasal steroids for OD related to AR. However, some studies demonstrate improvement in subjective olfaction scores and therefore antihistamines may be considered as an option to treat OD in AR.

In summary, OD is more common and more severe in CRSwNP compared to CRSsNP and AR.[4,6] Currently, there is strong evidence in the form of both subjective and psychophysical measures supporting use of oral steroids, dupiliumab, and omalizumab for OD in CRSwNP. There is also

support for the use of regular sustained topical steroid use for OD in CRSwNP, but this data is largely in the form of subjective outcomes. Oral steroids are generally used for short durations ranging from 1- 3 weeks and topical intranasal steroids are used for sustained longer term use. Biologics are used for prolonged periods at regular intervals (every 1-4 weeks) and olfactory benefit is unknown once the medication is stopped. These medications are recommended for the treatment of OD in CRSwNP in the appropriate clinical circumstances. Further high level studies investigating use of medical therapy for treatment of OD are needed, especially in CRSsNP and AR. (**Tables IX.3-17**)

Medical Therapy for Olfactory Dysfunction in CRSwNP

Table IX-3. Evidence for CRSwNP related olfactory loss management with oral corticosteroid therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Ecevit et al[29]	2015	2	RCT	CRSwNP (n=22) 1) PO Prednisolone 60 mg x 7 days followed by taper 2) Placebo	1) VAS (0-10) 2) BTS Data collection points: W2	Compared to placebo, prednisone group demonstrated significantly greater improvements in VAS and Butanol threshold tests at W2.
Banglawala et al[7]	2014	1	Systematic Review and Meta-analysis	CRSwNP (n=419) 5 RCTs with f/u ranging 12-48 wks	1) Subjective olfactory outcomes 2) Objective olfactory outcomes	Compared to placebo groups, oral steroid groups demonstrated significant improvement in both subjective and objective olfactory outcomes.
Alobid et al[30]	2014	2	RCT	CRSwNP (n=92) 1) PO Prednisone 30 mg	1) BAST Data collection points: W2, W12	Compared to baseline, only oral prednisone group demonstrated significant improvement at W2 &

				taper x 2 week + BUD NS 400 ug BID x 12 weeks 2) No rx (n=22)		W12.
Kirtsreesakul et al[31]	2012	2	RCT	CRSwNP (n=114) 1) PO Prednisone 50 mg OD x 2 weeks followed by MF NS 200 ug BID x 10 weeks 2) Placebo OD x 2 weeks followed by MF NS 200 ug BID x 10 weeks	1) Subjective sx score (0-3) Data collection points: W12	Compared to baseline, only oral prednisone group demonstrated significant improvement in subjective sx score at W12.
Alobid et al[32]	2012	2	RCT	CRSwNP (N=62) 1) PO prednisone 30 mg taper x 2 wks + BUD NS 400 ug BID x 12 weeks (n=46) 2) No rx (n=16)	1) Subjective Sx score (0-3) Data collection points: W2, W12	Compared to baseline, neither group demonstrated significant improvement.
Vaidyanathan et al[33]	2011	2	RCT	CRSwNP (n=60) 1) PO prednisolone 25 mg OD x 2 weeks + FP nasal	1) VAS (0-100) 2) Pocket smell test (PST) (0 – 3) Data collection points: W2,	Compared to placebo, the oral prednisolone group demonstrated significantly greater mean improvement in VAS (W2 only) and PST (W2 and W10).

				drops 400 ug BID x 8 weeks + FP NS x 18 weeks (n= 30) 2) Placebo tabs x 2 weeks + FP nasal drops 400 ug BID x 8 weeks + FP NS x 18 weeks (n=30)	W10, W28	
Van Zele et al[34]	2010	2	RCT	CRSwNP (n=47) 1) PO Methylprednisolone 32 mg taper x 20 days (n=14) 2) Placebo x 20 days (n=19)	1) VAS (0-10) Data collection points: W1, W2, W4, W8, W12	Compared to placebo, methyl prednisolone group demonstrated significantly greater improvement in VAS at W1, W2, and W4.
Benitez et al[35]	2006	2	RCT	CRSwNP (n=84) 1) PO Prednisone 30 mg OD taper x 2 weeks + BUD 400 ug BID x 10 weeks (n=63) 2) No rx (n=21)	1) Subjective sx score (0-3) Data collection points: W2, W12	Compared to baseline, only oral prednisone group demonstrated a significant improvement in subjective sx score at W2. This was not sustained at W12.
Wright et al[36]	2007	2	RCT	CRSwNP (n = 26) 1) PO prednisone 30 mg OD x 14 days + ESS(n=11)	1) VAS (0-10) Data collection points: W2, W4, W12, W24	Compared to baseline, only prednisone group demonstrated significant improvement in VAS at W2.

				2) Placebo + ESS (n =15)		
Alobid et al[37]	2006	2	Controlled clinical trial	CRSwNP (n=78) 1) PO Prednisone 30 mg taper x 2 weeks + BUD 400 ug x 48 weeks (n=60) 2) No rx (n = 18)	1) Subjective sx score (0-3) Data collection points: W12, W24, W48	Compared to baseline, only prednisone group demonstrated a significant improvement in subjective sx score at W12, W24, and W48.
Kroflic et al[38]	2006	2	Randomized comparative trial	CRSwNP (n=40) 1) PO Methylpednisolone (1mg/kg/day) x 7 days (n=20) 2) Nasal Furosemide (6.6 mmol/1 solution) (n=20)	1) Subjective sx score (0-3) Data collection point: W1	Compared to baseline, subjective sx scores improved significantly in both methylprednisolone groups and topical furosemide groups at W1. No significant difference in values post treatment when comparing groups.
Hissaria et al[39]	2006	2	RCT	CRSwNP (n=40) 1) PO Prednisolone 50 mg OD x 14 days (n=20) 2) Placebo x 14 days (n=20)	1) RSOM 31 (individual smell question) Data collection points: W2	Compared to baseline, only oral prednisolone group demonstrated significantly improvement in subjective smell at W2.

Oral Corticosteroids for olfactory dysfunction in CRSwNP

Aggregate Quality of Evidence: A (Level 1: 1 study, Level 2: 10 studies).
Benefit: Significant short-term improvements in subjective and objective measures of olfaction in CRSwNP patients. Duration of improvement with systemic corticosteroid alone may last 2-4 weeks, but this benefit may be lengthened with concurrent use of topical intranasal corticosteroids.

Harm: Corticosteroid risks include gastrointestinal upset, hyperglycemia, rare severe reactions, cataracts, increased risk of infection, transient adrenal suppression, insomnia, and increased bone turnover among others. Risks are greater with higher cumulative doses.
Cost:
Direct: Low monetary cost
Indirect: Minimal
Benefits-Harm Assessment: Preponderance of benefit over harm with short, infrequent treatment courses.
Value Judgments: Weighing the potential benefits against the possible harms should be done as part of a shared decision-making process.
Policy Level: Strong recommendation for short-term use.
Intervention: Strong recommendation for the use of oral corticosteroids in the **short-term** management of olfactory dysfunction in CRSwNP as part of a shared decision-making approach. Longer-term use of oral steroids for olfactory dysfunction in CRSwNP has not been studied and carries increased risk of harm to the patient.

Table IX-4. Evidence for CRSwNP related olfactory loss management with intranasal topical corticosteroid therapy

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Xu et al[40]	2020	2	RCT	CRSwNP (n=127) 1) PO Methylprednisolone 24mg OD + BUD NS 256 ug OD (n=44) 2) BUD nasal drops 1 mg OD and BUD NS 256 ug OD (n=41) 3) BUD NS 256 ug OD (n=42)	1) VAS (0-10) Data collection points: W1	Compared to baseline, all groups demonstrated improvement. No significant difference in post-treatment VAS score between groups.
Zeng et al[41]	2019	2	RCT	CRSwNP & CRSsNP (n=187) 1) FP NS 200ug OD 2) Clarithromycin 250 mg OD	1) VAS (0-10) Data collection points: M1, M3, M6, M12	Compared to baseline, both FP and Clarithromycin groups demonstrated significant improvement in VAS. But no significant

						difference between groups.
Khan et al[42]	2019	2	RCT	CRSwNP (n = 310) 1) MF NS 200mcg OD 2) MF NS 200 mcg BID 3) Placebo	Subjective sx score (0-3) Data collection points: M1, M4	Compared to placebo, only the MF NS BID dosing group demonstrated significantly greater improvement at M1 & M4.
Zhou et al[43]	2016	2	RCT	CRSwNP (n = 748) 1) MF NS 200 ug BID (n=375) 2) Placebo (n=373)	1) Subjective sx score (0-3) Daily diary Data collection points: W4, W8, W12, W16	Compared to placebo, MF NS group demonstrated significantly greater improvement in subjective sx score at all time points.
Chong et al[44]	2016	1	Systematic review of RCTs	RCTs (n=18) RCTs of CRSwNP (n=14) Analysis including dose, frequency and agent	1) Subjective measures of olfaction	The quality of the evidence was moderate for sense of smell
Bangwala et al[7]	2014	1	Systematic review and meta-analysis	A total of 28 randomized control trials evaluation olfaction in CRSwNP was identified and systematically reviewed.	1) Subjective olfactory outcomes 2) Objective olfactory outcomes	The results of this meta-analysis demonstrated that oral and topical steroids significantly improve olfaction in patients suffering from CRSwNP.
Janowski et al[45]	2009	2	RCT	CRSwNP (n=246) 1) FP NS 200 ug BID x 8 months, 2) FP NS 200 ug BID spray x 1 month, followed by FP NS 200ug OD + placebo OD x 7 months	1) VAS (0-100) 2) Mean sense of smell disorder score Data collection points: M1, M2, M8	Compared to placebo, both FP groups demonstrated significantly greater improvement in VAS (only at

				3) Placebo BID x 2 months, followed by FP NS 200 ug BD for 6 months		M1) and mean sense of smell disorder score (only M1 & M2).
Ehnhage et al[46]	2009	2	RCT	CRSwNP (n=68) 1) FP NS 400 ug BID spray 2) Placebo BID spray	1) Subjective sx score (0-3) 2) BTS Data collection point: W4	Compared to placebo, there was no significant benefit in the FP group.
Small et al[47]	2008	2	RCT	CRSwNP (n=447) 1) MF NS 200ug BID spray (n=224) 2) Placebo (n=223)	1) Subjective sx score (0-3) Data collection points: daily for 6.5 weeks	Compared to placebo, the MF group demonstrated significantly greater improvement in subjective sx score first on day 13 and remained significantly elevated throughout study duration.
Stjarne et al[48]	2006	2	RCT	CRSwNP (n=298) 1)MF NS 200ug OD spray (n=153) 2)Placebo (n=145)	1) Subjective sx score (0-3) 2) BTS Data collection points: W4, W8, W12, W16	Compared to placebo, MF group demonstrated significantly greater improvement in subjective symptom score and BTS at all time points.
Stjarne et al[49]	200	2	RCT	CRSwNP (n=310)	1) Subjective	Compared to

	6			1)MF NS 200 ug OD AM and placebo in PM (n=102) 2)MF NS 200 ug BD (n=102) 3)Placebo AM & PM (p=106)	sx score (0-3) Data collection points: W4, W12	placebo, MF 200ug BD dosing demonstrated significantly greater improvement in smell at W4. No significant benefit with QD dosing.
Aukema et al[50]	2005	2	RCT	CRSwNP (n=54) 1) FP NS 400ug OD (n=27) 2) Placebo (n=27)	1) VAS loss of smell (0-100) Data collection points: W2, W6, W12	Compared to placebo, FP group demonstrated significantly greater improvement in VAS at W12 only.
Small et al[51]	2005	2	RCT	CRSwNP (n= 1)MF NS 200ug OD (n= 115) 2)MF NS 200ug BID (n= 122) 3)Placebo (n= 117)	1) Subjective sx score (0-3) Data collection: W4, W12	Compared to placebo, both MF groups demonstrated significantly greater improvement in subjective sx score at W4 and W12.
Djikstra et al[52]	2004	2	RCT	CRS (n=162) underwent ESS followed by: 1)FP NS 400ug BID x 1 yr (n=53) 2) FP NS 800ug BID x 1 yr (n=53) 3) placebo BID x 1 yr (n=56)	1) VAS (0-100)	Compared to preop, there was significant improvement in VAS in all groups. Compared to placebo, there was no significant benefit in either FP groups.
Parikh et al[53]	2001	2	RCT	CRS (n=22)	Subjective sx score (0-3)	Compared to placebo, there

				1)FP NS (n=9) 2)Placebo (13)		was no significant benefit in subjective sx score in FP group.
Janowski et al[54]	2001	2	RCT (4 BUD groups vs placebo for 8 weeks)	CRSwNP (n=183) 1)BUD NS 128ug OD AM + Placebo PM x 8 weeks 2)BUD NS 128ug BID x 8 weeks 3)BUD NS 256ug OD AM + Placebo PM 4)Placebo x 8 weeks	1) Subjective sx score (0-4) Data collection: daily diary sx cards	Compared to placebo, all BUD treatment groups demonstrated significantly greater improvement in Subjective sx scores. Effect on symptoms became apparent within 1-2 days.
Keith et al[55]	2000	2	RCT	CRSwNP (n=104) 1)Nasal FP drops 400ug OD (n=52) 2)Placebo (n=52)	1) Subjective sx score (0-3) 2) UPSIT 3) BTS Data collection: W12	Compared to placebo, FP drops did not demonstrate significant benefit in any of the olfactory outcome measures.
Penttila et al[56]	2000	2	RCT	CRSwNP (n= 142) 1)FP NS 400ug BID (n=47) 2)FP NS 400ug OD (n=47) 3)Placebo (n=47)	1) UPSIT 2) BTS 3) Subjective sx score (0-3) Data collection points: W4, W8, W12	Compared to placebo, BID dosing demonstrated statistically significant improvement in UPSIT at one time point (not specified when). Compared to placebo, no significant

						benefit was noted on BTS or subjective sx score.
Mott et al[57]	1997	3	Cohort study	CRS (both polyp and non-polyp patients) 1) Nasal Flunisolide BD (n=45)	1) Subjective sx score (0-3) Data collection: between W8-W26	Compared to baseline, Significant improvement was noted.
Mastalerz et al[58]	1997	2	RCT	CRS (n=15) (all with aspirin sensitivity; 9 w/ polyps) 1)FP NS 200ug OD x 4 wks 2)Placebo OD x 4 wks	1) Subjective sx score (0-3) Data collection points: W1, W2, W3, W4	Compared to placebo, FP NS group demonstrated significantly greater improvement in subjective sx score at W2, W3, W4.
Lildholdt et al[59]	1995	2	RCT	CRSwNP (n=126) 1) Nasal BUD powder 200ug BID (n = 40) 2) Nasal BUD powder 400ug BID (n = 46) 3) Placebo (n = 42)	1) Subjective sx score Data collection points: W4	Compared to placebo, there was no significant benefit in BUD groups on subjective sx score.
Topical corticosteroid : Irrigation						
Huang et al[60]	2019	2	RCT	CRSwNP & CRSsNP 1) BUD nasal irrigation (n=30) 2) Saline irrigations (n=30)	1) VAS (0-10)	Compared to baseline, both groups demonstrated significant improvement. Compared to saline, BUD irrigation group did not demonstrate significantly greater improvement on VAS.

Harvey et al[61]	2018	2	RCT	CRSwNP & CRSsNP 1) MF nasal irrigation 2mg and Placebo spray OD (n=21) 2) Placebo Irrigation and MF NS 2mg OD (n=23)	1) VAS (0-100) Data collection points: M12	Compared to placebo, there was no significant benefit in Mometasone group on olfactory VAS score at M12
Rawal et al[62]	2015	2	RCT	CRSwNP (n=50) 1) Budesonide nasal irrigation 0.12mg BID (n=25) 2) Saline irrigations BID (n=25)	1) UPSIT 2) Phenethyl alcohol (PEA) test Data collection points: W1-2, W3-8, M3-M6	Compared to baseline, neither group demonstrated significant benefit on USPIT or PEA test at any time point.
Topical corticosteroid : Exhalation Driven Delivery						
Sindwani et al[63]	2019	2	RCT	CRSwNP (n=323) 1) FP EDS 327 ug BD x 24 wks (n=79) 2) FP EDS 186 ug BD x 24 wks (n=80) 3) FP EDS 93 ug BD x 24 wks (n=81) 4) Placebo EDS x 24 wks (n=82)	Subjective sx score (0-3) Data collection points: W4, W8, W12, W16	Compared to placebo, FP groups demonstrated significant greater benefit in olfactory subjective sx score at majority of time points.
Leopold et al[64]	2019	2	RCT	CRSwNP (n=323) 1) FP EDS 327 ug BD x 24 wks (n=82) 2) FP EDS 186 ug BD x 24 wks (n=80) 3) FP EDS 93 ug BD x 24 wks (n=80) 4) Placebo EDS x 24 wks (n=79)	1) Subjective sx score (0-3) Data collection points: W4, W8, W12, W16, W24	Compared to placebo, all FP EDS dosing groups demonstrated significantly greater benefit in subjective sx score at all time points.

Kobayashi et al[65]	2018	2	RCT	CRSwNP (n=23) 1) Exhaled HFA-134a-beclomethasone dipropionate via metered dose inhaler x 4 weeks 2) Placebo (n=12)	1) OSIT-J Data collection point: W4	Compared to baseline, both groups demonstrated significant benefit. Compared to placebo, exhaled corticosteroid group did not demonstrate any significant benefit.
Soteres et al[66]	2017	2	RCT	CRSwNP (n=323) 1) FP EDS 327 ug BD x 24 wks (n=82) 2) FP EDS 186 ug BD x 24 wks (n=80) 3) FP EDS 93 ug BD x 24 wks (n=80) 4) Placebo x 24 wks (n=79)	1) Subjective sx score (0-3) Data collection points: W4, W8, W12, W16, W24	Significant improvement compared to placebo at all time points and at all doses
Topical corticosteroid : Sinus Implant						
Kern et al[67]	2018	2	RCT	CRSwNP (n = 300) 1) Bilateral MF sinus implants + MF NS OD (n=201) 2) Sham placebo procedure + MF NS OD (n=99)	1) Subjective symptom sx (0-5) Data collection points: M3	Compared to placebo, MF sinus implant group demonstrated significantly greater improvement in subjective symptom score at M3.

Intranasal Topical Corticosteroids for olfactory dysfunction in CRSwNP

Aggregate Grade of Evidence: A (Level 1: 2 studies, Level 2: 26 studies, Level 3: 1 study).
Benefit: Significant improvements in subjective and objective measures of olfaction in CRSwNP patients. With regular use, benefits can be maintained.
Harm: Relatively low with epistaxis, nasal irritation, headache possible side effects.
Cost:

Direct: Low to moderate monetary cost depending on formulation.
Indirect: Minimal

Benefits-Harm Assessment: Preponderance of benefit over harm.

Value Judgments: Increasing dosage of topical intranasal corticosteroid should be considered if the magnitude of observed clinical benefit is partial/limited.

Policy Level: Strong recommendation for daily use of topical intranasal corticosteroid spray for the management of olfactory dysfunction in CRSwNP.

Intervention: The use of topical nasal corticosteroids for olfactory dysfunction in CRSwNP is strongly recommended both before and after sinus surgery.

Table IX.5. Evidence for CRSwNP related olfactory loss management with oral antibiotic therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Van Zele et al[34]	2010	2	RCT	CRSwNP (n=47) Study Arms 1) PO Doxycycline x 20 days (n=14) 2) PO Placebo x 20 days (n=19)	1) VAS (0-10) Data collection points: W1, W2, W4, W8, W12	Compared to placebo, doxycycline did not demonstrate significantly greater improvement in VAS at any time point.
Haxel et al[14]	2014	2	RCT	CRS (n=58) Study Arms 1) PO Erythromycin 250 mg daily (n=29) 2) PO Placebo (n=29)	1) SS (identification only) Data collection points: W2, W14, W26	Compared to placebo, there was no significant benefit noted in the Erythromycin group on SS at any time point.
Varvyanskaya et al[15]	2014	2	RCT	CRSwNP (n=66) Following ESS: Study Arms 1) MF NS (n=22) 2) PO Clarithromycin	1) SS 2) Data collection points: W6, W12, W24	Compared to baseline, all groups demonstrated significant improvement. Compared to control (MF

				250mg OD x 12 weeks (n=22) 3) PO Clarithromycin 250mg daily x 24weeks (n=22)		NS), Clarithromycin x 24 wk group was significantly improved on SS at w6 only. All remaining time points showed no no significant benefit in the clarithromycin groups.
Dabirmoghaddam et al[16]	2013	3	Cohort study	CRSwNP (n=40) Study Arm: 1) PO Clarithromycin 500mg BID for 8 weeks (n=40)	1) VAS (0-10) Data collection point: W8	Compared to baseline, significant improvement was noted.
Videler[17]	2011	2	RCT	CRSsNP (n=29) and CRSwNP(n=31) 1) PO Azithromycin 500mg OD for 3 days, then weekly for 11 weeks (n=30) 2) PO Placebo (n=30)	1) SS (identification only 2) VAS (0-10) Data collection points: W6, W12, W14	Compared to placebo, there was no significant benefit noted in the Azythromycin group on sniffin' sticks or VAS at any time point.

Oral antibiotics for olfactory dysfunction in CRSwNP

Aggregate Grade of Evidence: B (Level 2: 4 studies; Level 3: 1 study).
Benefit: No clear benefit in subjective or objective olfactory outcomes.
Harm: Relatively low, but adverse events in the medication groups included gastrointestinal upset, skin rash, insomnia, cardiotoxicity, hepatotoxicity, ototoxicity, and headache; Risks vary by antibiotic class and duration.
Cost:

Direct: Variable monetary cost depending on the antibiotic.
Indirect: Minimal

Benefits-Harm Assessment: Preponderance of harm over benefits.
Value Judgments: A lack of evidence and known adverse effects preclude routine use.
Policy Level: Recommendation against.
Intervention: Oral antibiotics should generally not be prescribed specifically to treat olfactory dysfunction in CRSwNP.

Table IX.6. Evidence for CRSwNP related olfactory loss management with Dupilumab

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Bachert et al [8]	2019	2	RCT	CRSwNP (n=448) 1) Dupilumab 300 mg Q 2 weeks x 52 weeks (n=150) 2) Dupilumab 300 mg Q 2 weeks x 24 weeks then Q 4 weeks X 28 weeks (n=145) 3) Placebo (n=133)	1) Subjective sx score (0-3) 2) UPSIT Data collection points: W52	Compared to placebo, Dupilumab arms demonstrated significant improvement in UPSIT and subjective sx score at W52.
Han et al [9]	2019	2	RCT	CRSwNP (n=276) 1) Dupilumab 300 mg Q 2 weeks x 24 weeks (n=143) 2) Placebo (n=133)	1) Subjective sx score (0-3) 2) UPSIT Data collection points: W24	Compared to placebo, Dupilimab arm demonstrated significant improvement in UPSIT and subjective sx sore at W24.
Bachert et al [10]	2016	2	RCT	CRSwNP (n=60) 1) Dupilumab 600 mg loading then 300 mg weekly for total of 16 weeks + MF NS (n=30) 2) Placebo + MF NS (n=30)	1) Subjective sx score (0-3) 2) UPSIT Data collection point: W16	Compared to placebo, Dupilumab arm demonstrated significant improvement in UPSIT and subjective sx score at W16.

Dupilumab for olfactory dysfunction in CRSwNP

Aggregate Grade of Evidence: A (Level 2: 3 studies)

Benefit: Dupilumab improves subjective and objective measures of olfactory dysfunction compared to placebo.

Harm: Conjunctivitis, injection site reactions, keratitis, and hypereosinophilia among others.
Cost:

Direct: High monetary cost per injection

Indirect: Relatively low with home injections

Benefits-Harm Assessment: Likely benefit over harm for olfactory dysfunction in patients with CRSwNP not responsive to traditional medical and surgical treatments.
Value Judgments: Benefits are lost if therapy is discontinued and costs are an important consideration.
Policy Level: Recommendation for use in patients with olfactory dysfunction related to severe CRSwNP.
Intervention: Dupilumab may be recommended for patients with olfactory dysfunction related to severe CRSwNP who have not improved despite other medical and surgical treatment options as part of a shared decision-making process.

Table IX-7. Evidence for CRSwNP related olfactory loss management with Mepolizumab

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Bachert et al[12]	2017	2	RCT	CRSwNP (n=105) 1) Mepolizumab 750 mg IV q 4 weeks for 24 weeks + FP NS 100ug OD (n=54) 2) Placebo +FP NS 100ug OD (n=51)	1) VAS (0-10) 2) Sniffin' Sticks (identification only) Data collection point: VAS: W1, W2, W5, W9, W13, W17, W21, W25 Sniffin' Sticks: W25	Compared to placebo, the Mepolizumab group did not demonstrate a significant benefit with Sniffin' Sticks at W25. Compared to placebo, Mepolizumab group demonstrated significantly greater improvement in VAS at W9 and this was sustained till W25.
Gevaert et al[68]	2011	2	RCT	CRSwNP (n=30) 1) Mepolizumab 750 IV x 2 doses only, 28 days apart (n=20)	1) Subjective sx score (0-3) Data collection point:	Compared to placebo, Mepolizumab group demonstrated a greater improvement

				2) Placebo (n=10)	W1, W4, W8, W12, W24, W36, W48	in subjective sx score, but this was not significant. Improvement was sustained till W48.

Mepolizumab for olfactory dysfunction in CRSwNP

Aggregate Grade of Evidence: B (Level 2: 2 studies)
Benefit: Mepolizumab appears to improve subjective olfactory symptom scores, but unclear if objective measures of olfaction improve.
Harm: Injection site reaction, eczema, flu-like symptoms, headache, muscle spasms among others.
Cost:

Direct: High monetary cost per injection
Indirect: Relatively low if home injections

Benefits-Harm Assessment: Balance of benefit and harm in those not responsive to traditional medical and surgical treatments.
Value Judgments: Benefits are lost if therapy is discontinued and costs are an important consideration. Consider for CRSwNP in context of asthma or EGPA; dosage used for trial in CRSwNP is higher than available for standard therapy of asthma and EGPA.
Policy Level: Option for use in patients with olfactory dysfunction related to severe CRSwNP
Intervention: May consider as option for olfactory dysfunction related to severe CRSwNP who have not improved despite other medical and surgical treatment options as part of a shared decision-making process.

Table IX-8. Evidence for CRSwNP related olfactory loss management with Omalizumab

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Gevaert et al[11]	2020	2	RCT	CRSwNP (n=138) Study arms: 1) Omalizumab 75-600mg q2-4w dosing (n=72) 2) Placebo (n=66)	1) Subjective sx score (0-3) 2) UPSIT Data collection points: W8, W16, W24	Compared to placebo, Omalizumab group demonstrated significantly greater improvement in subjective sx score and UPSIT at W8 and this was sustained to W24.

Gevaert et al[11]	2020	2	RCT	CRSwNP (n=127) Study arms: 1) Omalizumab 75-600mg q2-4w dosing (n=62) 2) Placebo (n=65)	1) Subjective sx score 2) UPSIT Data collection points: 1) W8, W16, W24	Compared to placebo, Omalizumab group demonstrated significantly greater improvement in subjective sx score and UPSIT at W8 and this was sustained to W24.
Gevaert et al[69]	2013	2	RCT	CRSwNP (n=24) 1) Omalizumab standard dosing x 16 weeks (n=16) 2) Placebo (n=8)	1) Subjective sx score Data collection point: W16	Compared to baseline, Omalizumab group demonstrated significantly greater benefit in subjective sx score at W16.
Pinto et al[70]	2010	2	RCT	CRSwNP (n=14) 1) Omalizumab standard dosing x 6 months (n=7) 2) Placebo (n=7)	1) Subjective sx score (0-3) 2) UPSIT Data collection point: M3, M5, M6	Compared to placebo, Omalizumab group did not demonstrate any significant benefit in regards to subjective sx score.

Omalizumab for olfactory dysfunction in CRSwNP

Aggregate Grade of Evidence: B (Level 2: 3 studies)

Benefit: Omalizumab improves subjective and objective olfactory measures of olfactory dysfunction compared to placebo.

Harm: Injection site reactions, cold symptoms, joint/muscle pain, risk for anaphylaxis (rare)

Cost:

Direct: High monetary cost per injection

Indirect: Variable depending on if home or in-office injections

Benefits-Harm Assessment: Likely benefit over harm for olfactory dysfunction in patients with CRSwNP not response to medical and surgical standard of care.

Value Judgments: Benefits are lost if therapy is discontinued and costs are an important consideration. Consider for CRSwNP with concomitant poorly controlled allergic asthma who have not improved despite other medical and surgical treatment options.

Policy Level: Recommendation for use in patients with olfactory dysfunction related to severe CRSwNP

Intervention: Omalizumab may be recommended for olfactory dysfunction related to severe CRSwNP who have not improved despite other medical and surgical treatment options as part of a shared decision-making process.

Table IX-9. Evidence for CRSwNP related olfactory loss management with Anti-leukotriene therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Stryjewska-Makuch et al[71]	2019	2	RCT	AERD (n=33) Following surgery: Study arms: 1) MF NS 200 ug BD 2) Montelukast 10 mg OD 3) MF NS 200 ug BD + Montelukast 10 mg OD	1) B-SIT Data collection point: M12	Compared to baseline, there was no significant benefit in B-SIT. There was no significant difference in B-SIT score at M12.
Van Gerven et al[72]	2018	2	Randomized, postoperative open-label trial	CRSwNP (n=72) Following surgery: Study arms: 1) MF NS 300ug TID (n=36) 2) MF NS 300ug TID + montelukast 10 mg OD (n=36)	1) BAST-24 2) VAS (0-4) Data collection point: M3, M6, M12	Compared to baseline, there was significant improvement in BAST score for both groups at all time points. Compared to baseline, MF NS only arms demonstrated significant benefit in VAS. No significant difference in VAS scores at M12.
Dahlen et al[73]	1998	2	RCT, cross-over	AERD (n=40)	1) VAS (0-10)	Compared to placebo, there

				1) PO Zileuton 600 mg QID + baseline standard therapy (n=40) 2) Placebo + baseline standard therapy (n=40)	Data collection points: W6	was a significant improvement in zileuton group on VAS at W6

Anti-Leukotriene Therapy for Olfactory Dysfunciton in CRSwNP

Aggregate Grade of Evidence: B (Level 2: 3 studies).
Benefit: No clear benefit on olfaction but data limited. Zileuton may have added benefit for subjective olfaction when used as an adjunct to INCS in AERD.
Harm: Montelukast has been associated with rare neuropsychiatric events in post-marketing reports. Zileuton may cause elevated liver enzymes requiring monitoring during therapy.
Cost:
Direct: Low to moderate monetary costs depending on formulation.
Indirect: Minimal
Benefits-Harm Assessment: Unclear given relative lack of available efficacy data.
Value Judgments: None
Policy Level: No recommendation.
Intervention: Lack of available data precludes a recommendation on anti-leukotriene used specifically for olfaction.

Table IX-10. Evidence for CRSwNP related olfactory loss management with Aspirin Desensitization therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Larivee et al[74]	2020	1	Systematic review	24 total studies (RCTs, case-control, cohort) and 1272 patients undergoing desensitization		15 studies with smell data, the majority indicating significant improvement compared to control
Swierczynska-Krepa et al[75]	2014	2	RCT	AERD (n=20) 1) ASA desensitization	1) VAS (0-10)	Compared to placebo, ASA desensitization

				followed by ASA 624mg (n=12) 2) Placebo (n=8)	Data collection point: M1, M2, M3, M4, M5, M6	group demonstrated significantly greater improvement in VAS at M1 & M6 only.
Fruth et al[76]	2013	2	RCT	AERD (n=31) Following surgery Study Arms: 1) ASA desensitization with 100 mg ASA over 3 years (n=18) 2) Placebo (n=11)	1) SS (identification only) Data collection: Y3	Compared to placebo, no significant benefit in ASA desensitization group was noted on SS at Y3.
Lee[77]	2007	2	RCT	AERD (n=137) Following ASA desensitization: 1) Discontinuation group 2) ASA 325 mg bid 3) ASA 650 mg bid	1) Subjective sx score (0-5) Data collection point: Y1	Compared to baseline, significant improvement in subjective sx score in all groups. There was no significant difference between groups
Cho[78]	2014	4	Retrospective cohort study	AERD (n=30) Following surgery patients underwent desensitization 1 mo postop 1) Maintenance dosing at either ASA 650mg qam and 325mg qhs 2) ASA 325mg BID	1) Subjective sx score (0-5) Data collection point: M1, M6, M12, M18, M24, M30	Compared to baseline, subjective sx score significant improvement at M1 and was sustained at M30

Aspirin Desensitization for Olfactory Dysfunction in AERD

Aggregate Grade of Evidence: B (Level 1: 1 study; level 2: 3 studies; level 3: 1 study).
Benefit: In AERD patients, ASA desensitization appears to improve olfactory dysfunction based on subjective measures. Limited objective data is available. Additional benefits include reduced need for future surgical intervention, less medication use, and fewer physician visits.

Harm: Gastrointestinal bleeding, increased morbidity in renal disease, and blood clotting issues at high maintenance doses among others. Estimated 3% gastrointestinal side effects with low-dose protocols.

Cost:

Direct: Moderate monetary cost of desensitization procedure. Minimal monetary costs of daily ASA use.

Indirect: Minimal

Benefits-Harm Assessment: Balance of benefit over harm.

Value Judgments: Aspirin desensitization followed by daily aspirin therapy is one of the very few disease-modifying medical treatment options available for patients with AERD. Benefits are typically most pronounced following sinus surgery.

Policy Level: Option for use in olfactory dysfunction related to AERD.

Intervention: Aspirin desensitization and daily therapy should be considered an option in AERD patients with olfactory dysfunction, particularly after surgical intervention.

Medical therapy for Olfactory Dysfunction in CRSsNP

Table IX-11. Evidence for CRSsNP related olfactory loss management with oral corticosteroid therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Liu et al[79]	2018	Case Series, retrospective	4	1) PO Antibiotics, mean 19 days (n=17) 2) PO Methylprednisolone for 6 days OR prednisone for 20 days (n=28) 3) Both PO antibiotics and oral steroids (n=55)	1) Loss of smell (yes or no)	Combination antibiotic and steroid demonstrated the best improvement in subjective loss of smell
Ikeda et al[80]	1995	Case series	4	PO Prednisolone, starting dose between 40-60mg for 10-14 days with a quick taper	1) Olfactory acuity tests	Significant improvement of olfactory detection and recognition.

Oral Corticosteroids for Olfactory Dysfunction in CRSsNP

Aggregate Quality of Evidence: C (Level 4: 2 studies).

Benefit: Benefit is unclear given limited investigation on oral corticosteroids in CRSsNP and lack of objective data. Corticosteroids appear to provide subjective improvement in small case series.

Harm: Corticosteroid risks include gastrointestinal upset, hyperglycemia, rare severe reactions, cataracts, increased risk of infection, transient adrenal suppression, insomnia, and increased bone turnover among others. Risks are greater with higher cumulative doses.

Cost:

Direct: Low monetary cost

Indirect: Minimal

Benefits-Harm Assessment: Not entirely clear due to lack of efficacy data, but possible benefits balanced with low risks with short, low-dose treatment course

Value Judgments: Clinicians should consider that many older patients may have smell loss independent of CRS.

Recommendation Level: Option

Intervention: The use of a short-term course of oral corticosteroid for olfactory dysfunction in CRSsNP is an option and should be individualized as part of a shared decision-making approach. Longer term use of oral steroids for olfactory dysfunction in CRSsNP has not been studied and carries increased risk of harm to the patient.

Table IX-12. Evidence for CRSsNP related olfactory loss management with topical corticosteroid therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Zeng et al[41]	2019	2	RCT	CRSwNP & CRSsNP (n=187) 1) FP NS 200ug OD 2) PO Clarithromycin 250 mg OD	1) VAS (0-10) Data collection points: M1, M3, M6, M12	Compared to baseline, both groups demonstrated improvement in VAS. But no significant difference between groups.
Harvey et al[61]	2018	2	DBRCT	CRS with and without polyps post ESS (n=44) 12 mo follow up 1) MF nasal irrigation 2mg (n=21) 2) MF NS 2mg (n=23)	1) VAS (0-100)	No significant different between spray and irrigation.
Zeng et al[81]	2011	2	RCT	CRSsNP (n=43) 1) MF NS 200ug OD spray X 12 weeks	1) Subjective sx score (0-3)	Compared to baseline, only Mometasone demonstrated significant

				2) PO Clarithromycin 250 mg tablet OD x 12 weeks Data collection point: W4, W8, W12	Data collection points: W4, W8, W12	improvement at W4 only. No significant improvement in clarithromycin group.
Hansen et al[82]	2010	2	RCT	CRSsNP (n=20) Bi-directional spray 12 week course of: 1) FP NS 400µg BID (n=10) 2) Placebo (n=10)	1) Subjective sx score (0-3) Data collection point: W12	Compared to placebo, FP group demonstrated significantly greater improvement in subjective sx score at W12.
Lund et al[83]	2004	2	RCT	CRS (n=167) 1) BUD NS 128ug BD x 20w 2) Placebo x 20w	1) Subjective sx score (0-3) (AM and PM) Data collection: W20	Compared to placebo, BUD group demonstrated significantly greater improvement in subjective sx score in AM only at W20
Djikstra et al[52]	2004	2	RCT	CRS (n=162) 1)FP NS 400ug BID x 1 yr (n=53) 2) FP NS 800ug BID x 1 yr (n=53) 3) placebo BID x 1 yr (n=56)	1) VAS (0-100)	Compared to preop, there was significant improvement in VAS in all groups. Compared to placebo, there was no significant benefit in either FP groups.
Parikh et al[53]	2001	2	RCT	CRS (n=22) 1)FP NS (n=9) 2)Placebo (13)	1) Subjective sx score (0-3)	Compared to placebo, there was no significant benefit in subjective sx score in FP group.
Mott et al[57]	1997	3	Cohort study	CRS (both polyp and non-polyp patients) 1)Flunisolide nasal	1) Subjective sx score (0-3)	Compared to baseline, there

				drops BID (n=45)	Data collection: between W8-W26	was significant improvement in subjective sx score.

Intranasal Topical Corticosteroids for Olfactory Dysfunction in CRSsNP

Aggregate Grade of Evidence: A (Level 2: 7 studies, Level 3: 1 study).
Benefit: The data is mixed with many studies failing to show a difference and a few showing modest improvement in subjective olfaction. There is very limited data on objective measures of olfaction.
Harm: Relatively low with epistaxis, nasal irritation, headache possible side effects.
Cost:
Direct: Low to moderate monetary cost depending on formulation.
Indirect: Minimal
Benefits-Harm Assessment: Balance of benefit and harm
Value Judgments: Data to support efficacy is significantly less robust compared to CRSwNP patients.
Policy Level: Option for the management of olfactory dysfunction in CRSsNP.
Intervention: Topical nasal corticosteroids are an option for olfactory dysfunction in CRSsNP before or after sinus surgery.

Table IX-13. Evidence for CRSsNP related olfactory loss management with oral macrolide antibiotic therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Deng et al[84]	2018	2	RCT	CRSsNP (n=32), CRSwNP (n=42) 3 months 1) PO Clarithromycin 0.25 g/d and BUD NS 256 µg OD 2) BUD NS 256 µg OD	1) VAS (0-10)	Compared to baseline, there was significant improvement in both groups. No difference between treatment groups.
Haxel et al[14]	2014	2	RCT	CRS 1) PO Erythromycin 250 mg daily (n=29) 2) Placebo (n=29) Total (n=58)	1) SS (identification only)	Compared to placebo, there was no significantly greater improvement in Erythromycin group.

				3 months		
Videler et al[17]	2011	2	RCT	CRSsNP (n=29) and CRSwNP(n=31) 1) Medical group (n=30): PO azithromycin 500mg OD x 3 days, then weekly for 11 weeks. 2) Placebo (n=30) 11 weeks	1) Sniffin' Sticks 2) VAS (0-3)	Compared to placebo, there was no significantly greater improvement in Azithromycin group.
Zeng et al[81]	2011	2	RCT	CRSsNP (n=43) 1) MF NS 200ug OD X 12 weeks 2) PO Clarithromycin 250 mg tablet OD x 12 weeks Data collection point: W4, W8, W12	1) Subjective sx score (0-3)	Compared to baseline, the Mometasone group demonstrated significant improvement at W4 only. There was no significant improvement in clarithromycin group.
Wallwork[85]	2006	2	RCT	CRSsNP without ESS 1) PO Roxithromycin 150mg OD (n=29) 2) Placebo (n=35)	1) SS	Compared to baseline, neither group demonstrated significant improvement. There was no difference between roxithromycin and placebo.

Macrolide Antibiotics for Olfactory Dysfunction in CRSsNP

Aggregate Grade of Evidence: B (Level 2: 5 studies).
Benefit: No clear benefit in subjective or objective measures of olfaction. Some studies demonstrate improvement in endoscopy and other CRS related symptom scores.
Harm: Gastrointestinal side effects, ototoxicity, hepatotoxicity, cardiotoxicity, and drug-drug interactions; potential microbial resistance.
Cost:
Direct: Low monetary cost
Indirect: Minimal
Benefits-Harm Assessment: Balance of benefit and harm.

Value Judgments: Optimal drug, dosage, and treatment duration are not known.
Policy Level: No recommendation.
Intervention: Lack of available data precludes a recommendation on macrolide therapy used specifically for olfaction.

Table IX.14. Evidence for CRSsNP related olfactory loss management with topical antifungal therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Ebbens et al[91]	2006	2	RCT	1) Nasal Amphotericin B 10 mg (n=59) 2) Yellow colored placebo (n=57)	VAS (0-100)	Compared to placebo, there was no significant benefit in topical antifungal group.
Yousefi et al[92]	2017	2	RCT	1) Nasal Amphotericin B 4 mg (n=40) 2) Placebo (n=40)	VAS (0-10)	Compared to placebo, there was no significant benefit of topical antifungal.
Jiang et al[93]	2018	2	RCT	1) Nasal Amphotericin B 20 mg (n=37) 2) Placebo (n=36)	UPSIT	Compared to placebo, there was no significant benefit of topical antifungal.

Topical Antifungals for Olfactory Dysfunction in CRSsNP

Aggregate Grade of Evidence: A (Level 2: 3)
Benefit: No apparent benefit from using topical antifungals
Harm: Treatment generally well tolerated with potential for local irritation; possible epistaxis and headache less common
Cost:
Direct: Moderate monetary cost
Indirect: Minimal
Benefits-Harm Assessment: Minimal risk of harm but no apparent potential for benefit
Value Judgments: The role in invasive fungal disease is not considered here.
Policy Level: Strong Recommendation Against

Intervention: Topical antifungal agents are not recommended for olfactory dysfunction related to CRSsNP

Medical therapy for Olfactory Dysfunction in AR

Table IX-15. Evidence for AR related olfactory loss management with antihistamine therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Klimek et al[18]	2017	3	Prospective multi-center observational study	AR (persistent) (n=47) 1)MP-AZE/FP NS BID for 3 months	1) Sniffin' Sticks	Compared to baseline, there was Significant improvement in olfactory function
Stuck et al [4]	2015	1	Systematic Review	AR 3 RCTs and 1 cohort study	1) Symptom scores 2) BAST 3) VAS	There is limited evidence that antihistamines improve olfactory function
Guilemany et al[86]	2012	2	RCT	AR (n=27) 1) PO Levocetirizine (5mg QD) 2) Placebo	1) BAST 2) VAS	Compared to placebo, Levocetirizine group demonstrated significantly greater improvement in VAS only after 7d
Kalpaklioglu et al[87]	2010	2	RCT	AR (n=62) 1) AZE NS 2) Triamcinolone NS	1) Subjectivesx score (0-3)	Compared to baseline, there was no significant improvement in either group. No significant

						difference between the 2 treatment arms.
Wober et al[88]	1997	4	Cohort study	AR (n=211 children) 1) AZE NS	1) Subjective sx score (0-3)	Compared to baseline, there was a significant increase in the number of symptom-free patients (smell loss)
Gambardella et al[89]	1993	2	RCT	AR (N=30) 1) PO Loratadine 2) Placebo	1) Subjective sx score (0-3)	No difference between the 2 treatment arms

Antihistamines for Olfactory Dysfunction in AR

Aggregate Grade of Evidence: B (Level 1: 1 study, Level 2: 3 studies, Level 3: 2 studies).
Benefit: There is limited evidence that antihistamines improve olfactory function in AR, with most studies showing no benefit. Further studies are needed.
Harm: Relatively low with dry mouth, drowsiness, dizziness, nausea, mood disturbance, confusion, urinary retention, and blurred vision possible side effects. Side effects are greater with first generation antihistamines and in elderly patients.
Cost:

Direct: Low to moderate monetary cost depending on formulation
Indirect: Minimal

Benefits-Harm Assessment: Balance of benefit and harm
Value Judgments: Second generation antihistamine recommended over first generation given central/sedating effects of first generation antihistamines
Policy Level: Option for treatment of olfactory dysfunction related to allergic rhinitis.
Intervention: Antihistamines are an option for use in treatment of olfactory dysfunction related to AR.

Table IX-16. Evidence for AR related olfactory loss management with intranasal topical corticosteroid therapy

Study	Year	LOE (1 to	Study Design	Study Groups	Clinical End-point	Conclusion

		5)				
Klimeck et al[18]	2017	3	Propsective multi-center observational study	Mixed AR (n=47) 1)MP-AZE/FP NS BID for 3 months	1) SS	Compared to baseline, there was significant improvement in olfactory function.
Dalgic et al[19]	2017	2	RCT	Seasonal AR (n=30) 1) Montelukast and MF NS (n=10) 2) Montelukast (n=10) 3) MF NS (n=10)	1) SS	Compared to baseline, Group 1 and 3 (those with MF) demonstrated significant improvement in SS. No significant improvement in TDI in montelukast group alone.
Stuck et al[4]	2015	1	Systematic Review	Mixed AR 1) 5 RCTs and 1 cohort study	1) UPSIT 2) VAS 3) Symptom score 4) CCCRC 5) Chemo-sensory specific quality of life 6) SS	Limited evidence that topical steroids improve sense of smell.
Higaki et al[90]	2012	2	RCT	Seasonal AR 1)MF NS 2) Placebo	1) Questionnaire	Compared to placebo, mometasone nasal spray did not demonstrate significant benefit.
Kalpakliogl u et al[87]	2010	2	RCT	Mixed AR (n=70) 1) AZE NS 2)Tramcinolone nasal spray	1) Symptom score	Compared to baseline, there was no significant improvement in either group. No significant difference between the 2

						treatment arms.
Sivam et al[20]	2010	2	RCT	Mixed AR (n=17) 1) MF NS 2) Placebo	1) Chemosensory-specific quality of life score 2) UPSIT	Compared to baseline, Mometasone group demonstrated significant improvement in chemosensory-specific quality of life but not UPSIT
Stuck et al[21]	2003	2	RCT	Seasonal AR (n=24) 1) MF NS 2) Placebo	1) SS 2) BTS	Compared to placebo, Mometasone group demonstrated significantly greater improvement on BTS
Meltzer et al[22]	1998	2	RCT	Mixed AR (n=121) 1) MF NS 2) Placebo	1) CCCRC	Compared to placebo, Mometasone group demonstrated significantly greater improvement in identification on CCRC
Golding-wood et al[23]	1996	4	Case series	Mixed AR (n=25) 1)Beclomethasone nasal drops	1) UPSIT 2) VAS	Compared to baseline, Beclomethasone drops demonstrated significant improvement in subgroup of patients with initial subjective olfactory impairment

Intranasal Topical Corticosteroids for olfactory dysfunction in AR

Aggregate Grade of Evidence: B (Level 1: 1 study, Level 2: 6 studies, Level 3: 2 studies).

Benefit: Data is mixed with some studies demonstrating benefit of INCS over placebo in subjective and objective measures olfactory function related to AR.
Harm: Relatively low with epistaxis, nasal irritation, headache possible side effects.
Cost:

Direct: Low to moderate monetary cost depending on formulation.
Indirect: Minimal

Benefits-Harm Assessment: Preponderance of benefit over harm
Value Judgments: Increasing dosage of topical intranasal corticosteroid should be considered if the magnitude of observed clinical benefit is partial/limited.
Policy Level: Recommendation
Intervention: Use of topical nasal corticosteroids is recommended for olfactory dysfunction related to AR.

Table IX-17. Evidence for AR related olfactory loss management with immunotherapy therapy

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Stuck et al[4]	2015	1	Systematic Review	Mixed AR 1 RCTs and 4 cohort studies	1) Subjective sx score 2) SS	Limited evidence that immunotherapy improves sense of smell.
Tansuker et al[24]	2014	4	Case series	Mixed AR (n=12) 1) SCIT	1) SS	Compared to baseline there was significant improvement on SS
Mun et al[25]	2013	4	Case series	Mixed AR (n=153) 1) SLIT	1) Subjective sx score	Compared to baseline, there was significant improvement in subjective symptom score
Kataotomic helakis et al[26]	2013	4	Case series	Mixed AR (n=36)	1) SS	Compared to baseline, there was significant improvement in subjective symptom score
Chang et al[27]	2009	4	Case series	Mixed AR (n=142) 1) SLIT	1) Subjective sx score	Compared to baseline, there was significant improvement in subjective symptom score

Radcliff et al[28]	1996	2	RCT	AR (n=36) 1) SCIT 2) Placebo	1) Subjective sx score	Superior to placebo

AERD = Aspirin exacerbated respiratory disease; AR = allergic rhinitis; ASA = Aspirin; AZE = Azelastine; BAST-24 = Barcelona smell test-24; BID = Twice daily; BSIT = Brief smell identification, BTS = Butanol Threshold Test; BUD = Budesonide; CCCRC = Connecticut chemosensory clinical research test; CRS = Chronic rhinosinusitis; CRSwNP = Chronic rhinosinusitis with nasal polyps; CRSsNP = Chronic rhinosinusitis without nasal polyps; EDS = Exhalation delivery system; ESS = endoscopic sinus surgery; FP = Flonase Propionate; MF = Mometasone Furoate; NS = Nasal spray; OD = Once daily; OSIT-J = Odor stick identification test for Japanese; PO = Per os; PST = pocket smell test; QOD-NS = Questionnaire of olfactory dysfunction-negative Statements; RCT = Randomized Controlled Trial; TID = Three times daily; SCIT = Subcutaneous immunotherapy; SLIT = Sublingual immunotherapy; SIT-40 = Smell identification test 40; SNOT22 = Sinonasal outcome test 22; SS = Sniffin' sticks; Sx = symptom; UPSIT = University of Pennsylvania smell identification test; VAS = Visual analogue scale

Immunotherapy for olfactory dysfunction in AR

Aggregate Grade of Evidence: B (Level 1: 1 study, Level 2: 1 study, Level 3: 4 studies).
Benefit: Improvement in subjective measures of olfactory dysfunction related to AR across most studies. Data is very limited with regard to objective measures.
Harm: Rare risk of severe anaphylactic reaction, higher in asthmatics and those on beta-blockers. Local reactions may be more frequent.
Cost:
Direct: Moderate cumulative monetary cost depending on regimen.
Indirect: Highly variable depending on frequency/duration of treatment and inconvenience to patient's daily life.
Benefits-Harm Assessment: Variable for each individual patient.
Value Judgments: The decision to begin immunotherapy is highly individualized and often driven by risks, direct costs, and convenience. A shared decision-making process is particularly important.
Policy Level: Option
Intervention: Immunotherapy is an option for olfactory dysfunction related to allergic rhinitis, particularly those unresponsive to more conservative medical management measures and deemed low risk.

SECTION: XI. Management
C. Treatment of underlying sinonasal inflammatory etiologies
2. Surgical treatment for CRS or AR-related olfactory loss

Surgical treatment of olfactory dysfunction (OD) related to chronic rhinosinusitis (CRS) and allergic rhinitis (AR) is primarily designed to improve the nasal airway, such that odorant-containing air can reach the olfactory cleft. Additionally, surgery might allow for more effective

delivery of topical medications that reduce mucosal inflammation.[1] Most of the available surgical literature focuses on olfactory outcomes following endoscopic sinus surgery in CRS. Although there are various surgical therapies for management of allergic nasal symptoms refractory to medical management, the available post-surgical olfactory outcomes data exists primarily for inferior turbinate surgery.[2–6]

In CRS, olfactory dysfunction is associated with the presence of polyps, asthma, diabetes mellitus and older age.[7] Endoscopic sinus surgery is usually considered after appropriate medical therapy has failed to control bothersome symptoms.[8] In most CRS studies investigating olfaction following endoscopic sinus surgery, patients are also treated with maintenance medical therapy (e.g., intranasal corticosteroid). Therefore, it is important to remember that recommendations for surgery assume ongoing medical therapy in most instances. The available clinical studies assess olfactory function through subjective measures (e.g., visual analogue scales, subjective symptom scores etc.) and objective psychophysical tests that include parameters such as forced-choice identification, smell discrimination, and olfactory thresholds. There are few randomized controlled trials investigating olfactory outcomes following surgical intervention in CRS/AR. Much of the available olfactory literature is comprised of prospective cohort studies or retrospective case series that focus on olfactory function following endoscopic sinus surgery. Recent meta-analyses found that sinus surgery improves nearly all subjective and objective measures of olfaction in CRS patients.[9,10] This benefit was most notable in patients with nasal polyposis and preoperative olfactory dysfunction. While further high-level studies are needed, endoscopic sinus surgery may be recommended in a patient with olfactory dysfunction related to CRS who has failed medical management. (**Table IX-18**)

The available evidence on olfactory function following inferior turbinate surgery in AR is very limited and is comprised of prospective cohort studies and retrospective case series. Additionally, many of the included studies look broadly at chronic rhinitis (CR) patients, but the majority of these CR cohorts are comprised of AR patients. While these studies demonstrate improvement in subjective measures of olfaction following turbinate reduction, the data on objective measures are mixed.[2,4] Although turbinate reduction is generally performed in AR

patients with nasal congestion refractory to medical therapy, no recommendation can be made for patients with AR-related OD due to the paucity of available evidence.

In summary, endoscopic sinus surgery is efficacious in treating OD related to CRS in patients who have failed medical therapy alone. Surgery should be part of a multimodal regimen that includes maintenance intranasal corticosteroids. Benefits are most notable for CRS with nasal polyps and those with poor preoperative olfactory function.[10] Evidence for surgical management of OD related to AR is extremely limited and further investigation is warranted. (**Table IX-19**)

Table IX-18. Evidence for CRS related olfactory loss management with endoscopic sinus surgery

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Zhao et al[9]	2020	2	Meta-analysis	Thirty-five studies including 3164 patients with CRS were eligible for the meta-analysis.	1) SS 2) SIT-40 3) VASBSIT 4) QOD-NS 5) B-SIT	ESS appears to be beneficial for improvement of olfactory function in patients with CRSwNP. Benefit is less clear in CRSsNP. Further thorough and comprehensive studies need to be conducted.
Moreno-luna R et al[11]	2019	3	Prospective cohort study	CRSwNP 1) ESS w/ mucoplasty (free mucosal graft to ethmoid) (n=10)	1)VAS(0-10)	No significant improvement in olfaction.
Zhang et al[12]	2019	4	Retrospective study	CRSwNP (n=40) 1)Eosinophilic polyps (n=21) 2)Non-eosinophilic polyps (n=19)	1)SS	Significant improvement in SS was noted. Fifty percent of patients improved by MCID (5.5).

Li et al[13]	2018	4	Retrospective study	1)CRSwNP (n=26)	1)VAS(0-10)	Improvement in VAS was noted.
Mattos et al[14]	2018	3	Observational, multi-center cohort study	1)CRS (n=128)	1)QOD-NS	Significant improvement in QOD-NS noted. MCID 5.2. Majority of patients reporting abnormal baseline QOD-NS achieved a MCID.
Walliczek-Dworschak et al[15]	2018	3	Prospective cohort study	1) CRSwNP (n=21)	1) SS 2) STS	Significant improvement in SS, but not STS.
Haxel et al[16]	2017	3	Prospective cohort study	1) CRS (n = 41)	1) SS	Significant improvement in SS.
Kohli et al[10]	2016	2	Meta-analysis	Mixed CRS patients	1) VAS 2) SNOT22 3) SIT-40 4) SS 5) B-SIT	Endoscopic sinus surgery improves nearly all subjective and objective measures of olfaction in chronic rhinosinusitis patients. Patients with nasal polyposis or preoperative olfactory dysfunction improve to a greater degree.
Andrews et al[17a]	2016	3	Prospective cohort study	1) CRSwNP (n=60) 2) CRSsNP(n=53)	1) SIT-40 2) Sense of smell VAS	Significant improvement in SIT-40 and VAS.
Chen et al[18]	2016	3	Prospective, single institute cohort study	1) CRSwNP (n=42)	1)VAS (0-10)	Significant improvement in VAS.
Lind et al[19]	2016	3	Prospective cohort study	1) CRSwNP (n=75) 2) CRSsNP (n=22)	1)SS	Significant improvement in SS.
Levy et al[20]	2016	3	Prospective, multi-institutional cohort study	1) CRS (n=122)	1)B-SIT	Significant improvement in BSIT. Greater in

						CRSwNP.
Soler et al[21]	2015	3	Prospective cohort study	1) CRS (n=121)	1) QOD-NS	Significant improvement in QOD-NS. Greatest improvement in patients with worse CT scores at baseline.
Ngyuen et al[22]	2015	3	Prospective study	1) CRSwNP (n=65)	1) VAS(0-10)	Significant improvement in VAS.
Ngyuen et al[23]	2015	3	Prospective study	1) CRSwNP (n=69)	1) SS	Improvement in olfactory function.
DeConde et al[24]	2015	3	Prospective study	1) CRS (n=311)	1) B-SIT	No significant improvement on B-SIT.
Kim et al[25]	2015	4	Cohort study	1) CRS (n=68)	1) VAS(0-10)	No significant improvement on VAS.
Kuperan et al[26]	2015	3	Randomized prospective single-blinded study	1) CRSwNP (n=17)	1) VAS(0-100) 2) SIT-40	Olfactory cleft surgery improves olfaction on SIT-40.
Hajjij et al[27]	2015	4	Nested case-control study	1) CRS(n=40)	1)B-SIT	No significant improvement in B-SIT.
DeConde et al[28]	2014	3	Prospective cohort study	CRS(n=280) 1)ESS (n=222) 2)Medical management (n=58)	1)B-SIT	Compared to baseline both groups improved. No significant difference between groups.
Jiang et al[29]	2014	4	Case-control study	1) CRSwNP (n=52) 2) CRSsNP (n=48)	1) SIT-40	No significant improvement in SIT-40
Katotomichelakis et al[30]	2014	3	Prospective study	1)CRS(n=116)	1)SS 2)QOD-NS	Significant improvement in SS and QOD
Minwegen et al[31]	2014	3	Prospective study	1)CRS (n=38)	1)SS	Significant improvement in SS
Baradaranfar et al[32]	2014	3	Non-randomized clinical study	CRS(n=60) 1)ESS followed by Fluticasone	1)Subjective sx score (0-10)	Compared to Fluticasone alone, ESS + Fluticasone group

				2)Fluticasone		demonstrated significant improvement
Murthy et al[33]	2013	3	Prospective observational study	1)CRS (n=71)	1)VAS	Significant improvement in VAS
Saedi et al[34]	2013	3	Prospective study	1)CRS (n=89)	1)SIT-40	Significant improvement in SIT-40
Schriever et al[35]	2013	3	Prospective study	1)CRS(n=113)	1)SS	Significant improvement on SS
Hsu et al[36]	2013	3	Cohort study	1)CRS(n=29)	1)SIT-40	Approximately 50% of patient demonstrated improvement in olfactory function
Saafan et al[37]	2013	2	Prospective randomized controlled trial	1)CRSwNP(n=17)	1)VAS(0-100)	Significant improvement on VAS.
Bhandarkar et al[38]	2011	3	Observational, prospective cohort study	1)CRS (n=142)	1)SIT-40	Significant improvement on SIT-40 for patients with osteitis.
Soler et al[39]	2010	3	Prospective study	1)CRS(n=101)	1)SIT-40	54.7% reported olfactory improvement of at least 4 points.
Katotomichelakis[40]	2010	3	Prospective study	1)CRSwNP(n=116)	1)SS	Significant improvement on SS.
Konstantinidis et al[41]	2010	3	Prospective study	1)CRSwNP (n=27)	1)SS	Improvement in SS in 74% of patients
Litvack et al[42]	2009	3	Prospective,multi-institutional cohort study	1)CRS (n=111)	1)SIT-40	Significant improvement in anosmics
Salama et al[43]	2009	3	Prospective cohort study	1)CRS(143)	1)VAS(0-10)	Significant improvement on VAS
Bugten et al[44]	2008	3	Prospective controlled trial	1)CRSwNP(n=57) 2)CRSsNP(n=45)	1)VAS(0-100)	Compared to baseline, there was significant improvement on VAS in both groups. No difference in degree of improvement between groups.

Konstantinidis et al[45]	2007	3	Prospective study	1)CRSwNP(n=18)	1)VAS(0-100) 2)SS	Significant improvement in SS and VAS.
Lee et al[46]	2007	3	Prospective study	1)CRSwNP(n=60)	1)VAS(0-10)	Significant improvement in pediatric and adult groups. No significant improvement in geriatric population.
Alobid et al[47]	2005	2	Randomized controlled trial	CRSwNP(n=109) 1) ESS followed by 12 months of intranasal Budesonide Prednisone x 2 weeks followed by 12 months of intranasal budesonide	1)Subjective sx score (0-3)	Compared to prednisone group, ESS group demonstrated significant improvement in sx score at 6 months. No difference at 12 months.
Blomqvist et al[7b]	2001	2	Randomized controlled trial	CRSwNP (n=32) with symmetrical nasal airways where each side was randomly assigned to ESS versus no ESS followed by local nasal budesonide. All patients received pretreatment with oral prednisolone for 10 days and topical budesonide for 1 month.	1) Butanol threshold test 2) VAS (0-10)	Compared to baseline, both sides improved. Compared to medical treatment side, there was no additional benefit noted with surgery.

BSIT = Brief smell identification, CRS = Chronic rhinosinusitis; CRSwNP = Chronic rhinosinusitis with nasal polyps; CRSsNP = Chronic rhinosinusitis without nasal polyps; ESS = endoscopic sinus surgery; QOD-NS = Questionnaire of olfactory dysfunction-negative Statements; SIT-40 = Smell identification test 40; SNOT22 = Sinonasal outcome test 22; SS = Sniffin' sticks; UPSIT = University of Pennsylvania smell identification test; VAS = Visual analogue scale

Endoscopic sinus surgery for olfactory dysfunction in CRS

Aggregate Grade of Evidence: C (Level 2: 5 studies; level 3: 30 studies; Level 4: 5 studies)

Benefit: Endoscopic sinus surgery appears to improve subjective and objective measures of olfaction in patients with CRS. This benefit is most notable in CRSwNP and those with severe baseline olfactory dysfunction.
Harm: Risks of endoscopic sinus surgery are considered low, but include bleeding, orbital injury, cerebrospinal fluid leak, and risks of general anesthesia.
Cost:
Direct: Moderate to high up-front monetary costs associated with sinus surgery and postoperative care
Indirect: Time required for procedure and recovery
Benefits-Harm Assessment: Benefit over harm, particularly in CRSwNP. Benefit to harm ratio less clear in CRSsNP and those with minimal baseline olfactory dysfunction.
Value Judgments: Candidates with worse baseline olfactory dysfunction and those with CRSwNP are more likely to benefit from ESS.
Policy Level: Recommendation
Intervention: As part of a shared decision-making process with a patient, it is reasonable to recommend endoscopic sinus surgery in a patient with olfactory dysfunction related to CRS who has failed medical management.

Table IX-19. Evidence for AR related olfactory loss management with turbinate surgery

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Hamerschmidt et al[5]	2016	3	Prospective cohort study	Chronic rhinitis (AR & NAR) (n=57) 1) Inferior turbinoplasty	1) Degree of smell improvement questionnaire	Majority of patients experienced "total improvement"
Assanasen et al[4]	2014	3	Prospective cohort study	Chronic rhinitis (AR & NAR) (n=48) 1) Radiofrequency inferior turbinate reduction	1) VAS 2) SDT	Significant improvement in VAS but not SDT
Garzaro et al[2]	2011	4	Case series	Chronic rhinitis (AR & NAR) (n=40) 1) RITR	1) SS	Significant improvement in SS
Parida et al[6]	2011	3	Prospective cohort	Perennial AR refractory to medical	1) VAS	Significant improvement in VAS

			study	management (n=50) 1) Radiofrequency volumetric tissue reduction		
Ikeda et al[3]	2006	3	Prospective case series	AR (n=56) 1) Functional inferior turbinosurgery and resection of posterior nasal nerve	1)VAS	Improvement noted in anosmics
AR = Allergic rhinitis; NAR = Non-allergic rhinitis; SDT = Smell detection threshold; SS = Sniffin' Sticks; VAS = Visual analogue scale						

Turbinate surgery for olfactory dysfunction in AR

Aggregate Grade of Evidence: C (Level 3: 4 studies; Level 4: 1 study).
Benefit: Five small studies which note improvement in subjective measures of olfaction in patients with AR. Two studies with objective data with mixed results. Overall data is very limited.
Harm: Relatively low risks, which include bleeding, infection, injury to adjacent structures, and risks of anesthesia
Cost:
Direct: Moderate monetary cost that varies based on site of care
Indirect: Low due to short recovery time after procedure
Benefits-Harm Assessment: Unclear given lack of data.
Value Judgments: None
Policy Level: No recommendation
Intervention: Turbinate reduction is typically performed in allergic rhinitis patients who complain of nasal congestion despite medical therapy. No recommendation can be made for patients with allergic rhinitis whose chief complaint is olfactory dysfunction.

SECTION: IX. Management
D. Treatment of intracranial, neurotransmitter, neurodegenerative diseases

Structural lesions, neurochemical imbalances, and accelerated neuronal death and neuroinflammation in olfactory processing regions can perturb odor-evoked processing, emotional response, and functional behavioral response. Medical treatment of olfactory

dysfunction (OD) related to intracranial disease (ICD), neurochemistry /neurotransmitter (NT) imbalances, and neurodegenerative disease (ND) is primarily designed to improve the central processing of odor-evoked neural activity. This activity arrives in the olfactory bulb from primary olfactory sensor neurons, where it is processed locally and then distributed to 5 distinct cortical areas for further processing: the piriform cortex, olfactory tubercle, entorhinal cortex, amygdala, and anterior olfactory nucleus.[1] The available clinical studies assess olfactory function through subjective measures (e.g., visual analogue scales or subjective symptom scores) and objective psychophysical tests that include parameters such as forced-choice identification, smell discrimination, and olfactory thresholds.[2]

OD related to ICD can be caused by structural lesions, such as the presence of tumors, aneurysms, and hemorrhages or by surgical procedures necessary to manage a structural lesion that in and of itself has not caused OD.[3] Both transcranial approaches (TCA) or endoscopic endonasal approaches (EEA) have been associated with subsequent olfactory dysfunction.[3] In most studies, investigating olfaction following TCA or EEA surgery, patients were treated with maintenance medical therapy (e.g., intranasal corticosteroid). Recommendations for surgery to treat intracranial disease assume a risk of olfactory dysfunction, and therapies for OD in this setting require further investigation.

There are limited controlled trials investigating medical therapy for OD from ICD, NT, or ND.[2] Only post-hoc cohorts were noted to improve in patients with post-traumatic anosmia (oral steroid pulse over 15 d) or PD (rasagiline). There is anecdotal data from a case report that olanzapine can mitigate parosmias and improve objective smell function in a patient with olfactory reference syndrome.[4] An aerobic exercise program stabilized the UPSIT score over 8 weeks relative to no exercise, although regression to the mean may account for this result.[5]

The available evidence on olfactory training is limited to neurodegenerative disease and is comprised of two prospective cohort studies and one clinical trial. While these studies demonstrate improvement in subjective measures of olfaction following smell training, the data on objective measures are mixed.[2] One study of Parkinson's disease (PD) patients tested olfactory training of the test odors vs. no training with same day and 1-2month follow-up. Significant improvement was noted in odor identification in the trained group vs. non trained

PD patients at both same day and 1 -2 month follow-up[9]. Performance on other odor tasks or identification of non-trained odors were not assessed. A recent meta-analysis of smell training found no significant improvement in smell function due to Parkinson's disease, although there was a trend towards improvement in odor discrimination[6]. Smell training improved olfactory function, which is associated with structural changes in the olfactory processing regions of the brain, in healthy individuals[7]. While further high-level studies are needed, smell training may be recommended in a patient with olfactory dysfunction related to IC, NT, and NG disease. Much of the available olfactory literature is comprised of prospective cohort studies or retrospective case series that focus on olfactory function as a diagnostic for neurodegenerative disease.

In summary, evidence for smell training and medical treatment for smell dysfunction in ICD, NT, and NG patients requires further study with double blinded trials to determine their efficacy. In the interim, empiric smell training protocols appear to be safe and can be considered in the appropriate clinical text for subjective and objective improvement, while patients undergo the specific medical or surgical treatments available for their specific underlying intracranial etiology.

Table IX-20. Evidence for smell training in ICD, NT, and ND related olfactory loss management

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Haehner et al[8]	2013	3	Prospective, controlled, non-blinded	PD patients underwent olfactory training BID for 12 weeks with 4 odorants (n=35). Controls (n=35).	Sniffin' Sticks (TDI) Threshold for 3 other trained odorants	Only significant difference was in total TDI (mean increase 2.4) and discrimination scores. 20% vs. 9% met MCID. Independent of age, sex, severity, duration of disease.
Knudsen et al[9]	2015	3	Prospective,	PD patients -smell	Sniffin'	Improvement in

			nonblinded, cohort study	re-training of odors on the test (n=34); healthy controls-smell retraining (n=26); PD patients-no training (n=20) Training consisted of one session of 2 ten-minute exposures to the SS odors with visual and written cues	Sticks (identification) Measured pre and immediately post training. Retest in 8 after 4-8w.	identification (increase of 2.2) was noted same day. Benefit persisted at retest.

ICD = intracranial disease; ND = Neurodegenerative Disease; NT = Neurotransmitter; OI = odor identification; SS = Sniffin' sticks

Smell training therapy for olfactory dysfunction in intracranial, neurotransmitter, and neurodegenerative disease

Aggregate Grade of Evidence: C (Level 2: 1 studies; level 3: 2 studies)
Benefit: Smell training may improve subjective and objective measures of olfaction in patients with ND causes of smell loss.
Harm: Very low – very small risk of allergy to smells in training kit
Direct: Small up-front monetary costs associated with assembly of smell training kit and tests to assess progress
Indirect: Time required for procedure
Benefits-Harm Assessment: Benefit over harm, particularly in Parkinson's disease.
Value Judgments: As part of a shared decision-making process with a patient, it is reasonable to recommend smell training in a patient with olfactory dysfunction related to neurodegenerative diseases
Policy Level: Option
Intervention: Consider smell training in a patient with olfactory dysfunction related to neurodegenerative disease given very low risk.

Table IX-21. Evidence for medical therapy for ICD, NT, and ND olfactory loss management

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion

Haehner et al[11]	2013	2	Single-center, prospective, randomized, controlled, double-blind	Patients with diagnosis of PD: rasagiline 1mg OD for 120 days (n=17), placebo (n=17)	1) Sniffin' Sticks (TDI) 2) Retronasal testing 3) Olfactory Event Related Potential (OERP)	No significant improvement for any component of TDI score, retronasal testing or OERP
Haehner et al[12]	2015	4	Single center, cross sectional	Patients with diagnosis of PD (n=224): rasagiline 1mg QD (n=74), controls (n=150)	Sniffin' Sticks (TDI)	No significant difference for TDI score or any subcomponent. Treated patients with disease <8 years had better discrimination.
Dhilla Albers et al[4]	2018	4	Case Report	1) ORS (n = 1)	1) Percepts of Odor Episodic Memory (POEM) olfactory battery	Improvement in symptoms and OI with treatment of olanzapine.
Rosenfeldt et al[5]	2016	3	Single site, unblinded, placebo-controlled trial	Patients diagnosed with Parkinson's disease: aerobic exercise (n=23), placebo (n=15)	UPSIT	Stabilization of UPSIT over 8 weeks of exercise relative to controls (3 point decline of over 8 weeks).
Aromha = Accessible, remote, olfactory-mediated health assessment; B-SIT = Brief Smell Identification Test; ICD = intracranial disease; ND = Neurodegenerative Disease; NT = Neurotransmitter; OI = odor identification; ORS = Olfactory Reference Syndrome; PD = Parkinson's disease; TDI = Threshold, Discrimination, Identification; SS = Sniffin' Sticks; UPSIT = University of Pennsylvania Smell Identification Tes; VAS = Visual analogue scale						

Medical therapy for olfactory dysfunction in ICD, NT, and ND related disease

Aggregate Grade of Evidence: C (Level 2: 1 study; Level 3: 3 studies; Level 4: 2 studies).
Benefit: One case report notes improvement in subjective measures of olfaction in patients with dysomias with olanzapine. Two studies with objective data with mixed results. One study notes stabilization of UPSIT in PD patients with an aerobic exercise program. Overall data is very limited.
Harm: Olanzapine carries black box warning of increased risk of stroke and death in elderly patients.
Cost:
Direct: Moderate monetary cost that varies based insurance provider
Indirect: Low
Benefits-Harm Assessment: Unclear given lack of data.
Value Judgments: None
Policy Level: No recommendation
Intervention: No recommendation can be made for patients with post-iatrogenic anosmia, Parkinson's disease, ORS, or dysosmias given lack of clear benefit and risks associated with prescription medicine. Aerobic stationary bicycle exercise can be recommended to patients with Parkinson's disease for many reasons and may slow the decline of smell loss.

SECTION: XI. Management
E. Treatment of other underlying systemic disease states

One of the less discussed areas of olfactory dysfunction is the management of olfactory dysfunction due to underlying systemic diseases. In this area, three main systemic causes emerge: hormonal diseases, autoimmune diseases and vitamin and mineral deficiencies.

Treatment of Olfactory Dysfunction Related to Endocrine and Metabolic Diseases

Diabetes mellitus (DM) is the most common cause of olfactory dysfunction among hormonal diseases.[1] Several mechanistic hypotheses have been suggested, including elevated Hemoglobin A1c (Hba1c) levels, microvascular and macrovascular complications, and polyneuropathies.[1,2] A strong association between olfactory dysfunction and increased risk of cognitive impairment has been reported in Type 2 DM.[3,4] In general, studies have revealed that

type 2 DM with complications is associated with olfactory dysfunction, while uncomplicated type 1 DM is not.[5,6] Therefore, prevention of diabetic complications plays an important role in the treatment of olfactory dysfunction in these patients. Interestingly, hyperbaric oxygen therapy used in the adjuvant treatment of diabetic neuropathy significantly increased olfactory function scores.[7]

Thyroid diseases are also important causes of olfactory dysfunction among endocrine diseases, most commonly hyposmia in hypothyroidism.[8] It is thought that the main reason for the development of hyposmia in hypothyroid patients is the role of thyroid hormone in olfactory receptor maturation.[9] Thyroid hormone replacement provides significant olfactory improvement in patients with frank hypothyroidism as well as subclinical hypothyroidism.[10,11]

Obesity has recently become associated with metabolic olfactory dysfunction and studies have shown that a loss of odor sensitivity is associated with an increase in body weight.[12] Therapeutically, mixed results have been reported with weight loss surgery. One study of gastric bypass patients demonstrated a positive effect on taste, but not on olfaction.[13] In a later similar study, weight loss surgery was able to return olfaction, and taste recovered to normal levels six months post procedure.[14]

Treatment of Olfactory Dysfunction Related to Autoimmune Diseases

Autoimmune diseases have long been associated with smell loss.[15,16] Specifically, Sjogren's Syndrome and Systemic Lupus Erythematosus (SLE) have been found to commonly exhibit olfactory deficits. Schonfeld et al. reported that the odor threshold and odor discrimination scores decreased in patients with SLE, and that olfactory dysfunction correlated with disease severity and central nervous system involvement.[17] SLE is a chronic autoimmune disease that requires long-term immunosuppressive therapy and causes neurocognitive damage due to both the disease and the side effects of the treatments. Bombin et al. found that factors such as inflammation and duration of illness with SLE, as well as secondary anxiety and depression, usually mandates multidisciplinary evaluation in these patients.[18] Another important cause of olfactory disorders among autoimmune diseases is IgG4-related disease (IgG4-RD), which has been associated with type 1 autoimmune pancreatitis, chronic sialoadenitis, kidney disease,

periaortitis, and dacryoadenitis.[19] Yagi-Nakanishi et al[20] found that 52% of these patients had olfactory dysfunction. Likewise, olfactory dysfunction was found in Mikulicz's disease restricted to the salivary glands, which is also thought to be an IgG4-related disease and was found specifically in patients with increased IgG4 plasmacytes in the nasal mucosa.[21] It has been demonstrated that steroids are very effective in the treatment of IgG4-RD, helping to reverse associated epithelial damage as well as central nervous system dysfunction.[20]

Treatment of Olfactory Dysfunction Related to Mineral and Vitamin Deficiency

For many years, the questions of whether zinc deficiency can cause olfactory dysfunction and whether zinc replacement can be a useful treatment option have been investigated.[22] It is now known that zinc deficiency only rarely causes olfactory dysfunction, but it is much more commonly associated with taste deficits that typically reverse with zinc replacement.[23,23a] On the other hand, intranasal zinc, applied in a high concentration topical solution, has long been used as an experimental model of temporary olfactory loss in animals.[24] This concept was adapted as a means of chemoprophylaxis against polio in the era prior to vaccination. Topical intranasal zinc, in high concentration, was applied to the olfactory cleft during pandemics to induce temporary anosmia in an attempt to reduce spread of the virus to the CNS, as it was assumed (incorrectly) that the olfactory nerves were the portal of entry.[25] Although the majority of the children recovered their sense of smell, there were anecdotal reports of permanent smell loss.[26] More recently, OTC topical intranasal zinc sprays were marketed to treat the common cold but later implicated in the development of anosmia based on 2 case series with some overlapping patients.[27,28] The product was ultimately pulled from the market. The dose of zinc delivered by this product was extremely low relative to that used in animal studies and human polio trials, access to the olfactory cleft very limited with the spray, and the well-established cause of typical post-viral anosmia, hard to exclude.[29] Nevertheless, intranasal medications can damage the olfactory mucosa and this possibility needs to be considered with the development of intranasal drugs in general.

Vitamin A has significant effects on epithelial differentiation and it was considered a promising agent to treat peripheral olfactory loss, especially if patients may have an underlying deficiency. In the only known study examining a population of patients known to be deficient in Vitamin A, high dose replacement did appear to have beneficial effect on olfactory function.[29a] In contrast, when no deficiency is noted, Vitamin A, given systemically at the dose of 10,000 IU per day for 3 months, was reported to be ineffective on reversing olfactory loss.[30] Five years after this initial study however, Vitamin A applied intranasally as an add-on treatment in conjunction with olfactory training, was suggested to be effective for the treatment of post-infectious olfactory loss, but this study was an uncontrolled, unblinded, retrospective study, disallowing for any conclusion about true efficacy in a non-deficient patient population.[31]

Iron deficiency is also associated with olfactory deficits[32] that improved with iron replacement.[33] Vitamin B12 deficiency is also a cause of reversible olfactory dysfunction, as well as mild cognitive impairment.[34] Consequently, it is possible that the correction of vitamin B12 deficiency improves olfaction via the reversal of the mild deficit in neurocognitive processing.[35,36]

Vitamin B1, (thiamin) replacement has been found to be effective in the management of smell loss due to Parkinson's Disease (PD). Haglin et al. Reported that thiamine and folic acid deficiency in the diet, especially 2 to 8 year prior to the diagnosis of PD, led to olfactory dysfunction.[37] It was suggested by Heilmann at al. that vitamin B1 deficiency causes odor loss and that longterm replacement can be an effective treatment.[38] In this study, Vitamin B treatment was compared with local and systemic corticosteroid treatments. Patients with many causes of olfactory dysfunction such as post-infectious, posttraumatic, sinonasal and idiopathic causes were included in this study. Vitamin B treatment, which was noted to be ineffective in the first 2 months, was found to be an effective treatment method when extended to 6 months, however with such a heterogeneous patient population, enrollment of patients as early as one month post-smell loss, no control or placebo, no definitive conclusion can be made. While discussing the olfactory effects of B vitamins, Thiamine (B1), Pyridoxine (B6) and Methylcobalamin (B12), it is absolutely necessary to consider homocysteine. Homocysteine, an

amino acid synthesized from the amino acid methionine, has a key role in vitamin B metabolism. If there is an increase of homocysteine in the body, vitamin B deficiency is likely present. In addition, homocysteine levels increase with age and with increasing oxidation in the body, so homocysteine may be a cause of olfactory dysfunction, both directly and indirectly via secondary vitamin B deficiency.[39]

While examining the effects of vitamins and minerals on olfactory function, their mutual interactions and metabolism should not be overlooked, and in addition, various common mutations (such as methyl tetra folate reductase enzyme mutation) (MTHFR mutations) will cause differences in homocysteine metabolism and subsequent changes in vitamin B metabolism.[40]

In conclusion, the treatment of olfactory dysfunction secondary to endocrine, metabolic, autoimmune, vitamin and mineral deficiency should be based on the treatment of the primary disorder.

Table IX-22. Evidence Summary Table: Treatment of other underlying Endocrine Disease

Study	Year	LOE	Disease	Study Design	Study Groups	Clinical Endpoint	Conclusions
Weinstock et al[1]	1993	3	Diabetes Mellitus	Cohort	(n=111) Patients with diabetes mellitus (DM)	Olfactory function (Odorant Confusion Matrix)	The presence of macrovascular disease in DM was found to be associated with olfactory dysfunction.
Brady et al[2]	2013	2	Diabetes Mellitus	Double-blinded, placebo controlled -crossover study	(n=74) participants, (19 Healthy) with DM	Olfactory function (Sniffin' Sticks)	The presence of neuropathic pain in DM was found to be associated with olfactory dysfunction.
Sanke et al[3]	2014	3	Diabetes Mellitus	Cohort	(n=250) patients, with Diabetes Mellitus	Olfactory and Cognitive functions (Open Essence Test, Minimental	The Olfactory Essence test Score of the probable dementia group with

						State Examination)	Type 2 DM significantly lower than other groups.
Yulug et al[4]	2020	2	Diabetes Mellitus	Double-blinded, placebo controlled -crossover study	(n=46) participants, 16 prediabetic, 15 Type 2 Diabetes Mellitus	Olfactory and Cognitive functions (Sniffin' Sticks, Minimental State Examination)	The Olfactory and Cognitive test scores different in Diabetes and Prediabetes groups. There is a strong association between olfactory dysfunction and specific memory impairment in a population with prediabetes and diabetes.
Altundag et al[5]	2017	2	Type 1 Diabetes Mellitus	Double-blinded, placebo controlled -crossover study	(n=70) participants, 31 healthy controls, 39 non-complicated Type 1 Diabetes Mellitus	Olfactory and Gustatory functions (Sniffin' Sticks, Taste Strip)	The Olfactory and Gustatory functions scores did not decrease in non complicated Type1 DM
Gouveri et al[6]	2014	2	Type 2 Diabetes Mellitus	Double-blinded, placebo controlled -crossover study	(n=154) participants, 119 Type 2 Diabetes Mellitus	Olfactory functions (Sniffin' Sticks)	Diabetic Complications were associated with olfactory dysfunction.
Veyseller et al[7]	2016	4	Type 2 Diabetes Mellitus	Cohort	(n=62) participants, 30 healthy controls	Olfactory functions (Connecticut Chemosensory Clinical Research Center Test)	Diabetic Neuropathy leads to diabethic olfactopathy. Hyperbaric oxygen treatment can be used on diabetic olfactopathy.

McConnell et al[8]	1975	4	Hypothyroidism	Case Series	(n=18) Hypothyroid patients	Olfactory and Taste functions (Taste Solutions, Pyridine-Nitrobenzene for olfactory functions)	Untreated hypothyroidism leads to olfactory and gustatory dysfunction reversible with thyroid hormone replacement.
Günbey et al[9]	2015	3	Hypothyroidism	Cohort	(n=90) 45 primary Hypothyroid patients	Olfactory function (Sniffin' Sticks)	Free T3 levels were found to have a more significant relationship with olfactory parameters than TSH or Free T4 levels.
Baskoy et al[11]	2016	3	Hypothyroidism / 3 months L-thyroxine treatmen	Cohort	(n=59) 28 Subclinical Hypothyroid patients	Olfactory and Gustatory function (Sniffin' Sticks, Taste Strips)	Subclinical hypothyroid patients exhibited a significantly decreased olfactory sensitivity correctable with treatment. Bitter taste positively correlated with T3 with treatment.
Peng et al[12]	2019	4	Obesity	Review	(n=19) Observational and Clinical Studies	Meta analysis of olfactory function with Sniffin' Sticks	There is strong evidence for the link between olfactory loss and obesity. Bariatric surgery is effective in reversing obesity and associated OD.
Richardson et al[13]	2012	3	Obesity	Cohort	(n=95) 55 patients Gastric Bypass Surgery	Olfactory function (Cross Cultural Smell	Gastric Bypass Surgery does not appear to infuence

						Identification Test)	olfactory function.
Holinski et al[14]	2015	4	Obesity	Case Series	(n=44) Morbidly Obese Patients undergoing Bariatric Surgery	Olfactory and Gustatory functions (Sniffin' Sticks, Taste Strips)	Both olfactory and gustatory functions improve 6 months after bariatric Surgery.

Investigating the treatment of metabolic and endocrinologic diseases in patients to improve OD

Aggregate Grade of Evidence: C (Level 2: 4 studies; Level 3: 5 studies; Level 4: 4 studies)

Benefit: In patients with olfactory dysfunction, evaluation for metabolic and endocrinologic diseases may potentially help diagnose the reason for olfactory dysfunction. The correction of hypothyroidism, preventing complications with DM, and weight loss after bariatric surgery can lead to improvements in OD associated with these underlying systemic diseases after treatment.

Harm: Known potential side effects and adverse events associated with medical and surgical treatments aimed at correcting these underlying diseases.

Cost: Cost of medical or surgical treatments

Benefits-Harm assessment: Potential prevention of other systemic complications of hypothyroidism, diabetes mellitus, and obesity.

Value Judgments: Endocrine and metabolic diseases can cause olfactory dysfunction and correcting these can correct OD.

Policy level: Evaluating and treating patients with olfactory disorders and suspected or known diabetes, hypothyroidism or obesity is **recommended**.

Intervention: Laboratory tests, including serum TSH, glucose and Hg A1c levels should be considered in individuals with OD and suspected hypothyroidism or diabetes, and referrals to specialists who can treat these underlying disorders should be made.

Table IX-23. Evidence Summary Table: Treatment of other underlying Autoimmune Disease

Study	Year	Level of Evidence	Disease	Study Design	Study Groups	Clinical Endpoint	Conclusions
Perricone et al[15]	2013	4	Autoimmunity-Systemic Lupus Erythematosus	Review	Articles about autoimmunity and smell	Relationship between autoimmune diseases and olfactory function	Olfactory Receptor gene clusters close to MHC complex

Strous et al[16]	2006	4	Autoimmune Disorders	Review	Articles about autoimmunity and smell	Olfaction and Immune system	Olfactory system has a strong link with immune system
Shoenfeld et al[17]	2009	2b	Systemic Lupus Erythematosus (SLE)	Cohort	(n=100) participants , 50 SLE	Olfactory function (Sniffin' Sticks)	Olfactory function decreased in SLE patients.
Bombini et al[18]	2017	2b	Systemic Lupus Erythematosus (SLE), Systemic Sclerosis	Cohort and Review	(n=366) participants , 143 SLE patients.	Olfactory function (Sniffin' Sticks)	Olfactory function decreased in SLE and Systemic syclerosis patients.
Stone et al[19]	2012	2b	IgG4-Related Disease	Cohort and Review	Review Article	Mechanism of Disease	Multiple immune-mediated mechanisms contribute to the inflammatory processes of IgG4-related disease
Yagi-Nakanishi et al[20]	2016	4	IgG4-Related Disease	Case series	(n=25) patients with IgG4-related disease	Olfactory function (T&T olfactometer)	Olfactory dysfunction is an important manifestation of IgG4-related disease and may be reversible.
Takano et al[21]	2011	4	Mikulicz's Disease (also an IgG4 disease)	Case series	(n=44) patients with Mikulicz's disease	Olfactory function (T&T olfactometer)	Olfactory dysfunction may be associated with infiltration of nasal mucosa by IgG4-positive plasmacytes in Mikulicz's disease.

Investigating and treating autoimmune diseases in patients with related OD

Aggregate Grade of Evidence: C (Level 2b: 3 studies; Level 4: 4 studies)

Benefit: In patients with olfactory dysfunction, evaluation for autoimmune diseases, especially Sjogren, Systemic Lupus Erythematosus (SLE) and IgG4 related disease may potentially help with diagnosis and treatment.

Harm: Known potential side effects and adverse events associated with medical treatments.
Cost: Cost of medical treatments aimed at underlying disorder.
Benefits-Harm assessment: May prevent other systemic complications of autoimmune diseases
Value Judgments: Autoimmune diseases can cause olfactory dysfunction and treatment of the underlying disease process may help correct both OD as well as other associated symptoms.
Policy level: Evaluating and treating patients with olfactory disorders related to suspected or known autoimmune diseases is **recommended**.
Intervention: Laboratory tests, including serum autoimmune markers should be considered in individuals with OD and suspected underlying autoimmune disease.

Table IX-24. Evidence Summary Table: Treatment of underlying Vitamin Deficiency

Study	Year	Level of Evidence	Disease	Study Design	Study Groups	Clinical Endpoint	Conclusions
Henkin et al[22]	1975	4	Zinc Deficiency due to histidine administration to treat Progressive Systemic Sclerosis	Case Series	(n=6) patients with Progressive Systemic Sclerosis taken histidine aminoacid, 4 female 2 male patients.	Single olfactory and gustatory function tests (pyridine for smell, urea for taste)	Acute zinc loss due to histidine treatment cause olfactory and Gustatory dysfunction and treated rapidly with zinc administration.
Jafek et al[27]	2004	4	Anosmia after zinc gluconate	Case series	N=10	Colorado CS questionaire	Zinc induced anosmia occurs after exposure to olfactory epithelium
Alexander and Davidson[28]	2006	4	Zinc Induced Anosmia Syndrome	Case Series	(n=17)	UPSIT	Zinc induced anosmia occurs after the exposure of zinc cation to olfactory epithelium

Garrett-Laster et al[29a]	1984	4	Vitamin A deficient patients (n=27) treated with oral vitamin A (10,000 micrograms/d) for 4 weeks	Descriptive (non-controlled) study	Pyridine detection and recognition threshold improvement	Significant improvement in olfactory threshold	Garrett-Laster et al[29a]
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Reden et al[30]	2012	2	Postinfectious, Posttraumatic anosmia treatment with systemic vitamin A	Double-blind randomized, plasebo-controlled clinical trial	(n=52) patients (26 placebo, 26 systemic Vitamin A, 10.000 IU , 3 months)	Olfactory function (Sniffin' Sticks)	Systemic application of vitamin A not useful for treatment of postinfectious or posttraumatic olfactory loss.
Hummel et al[31]	2017	4	Postinfectious anosmia treatment with smell training and intranasal vitamin A	Retrospective Cohort	(n=170) patients (46 only smell training, 124 smell training+intranasal Vitamin A, 10.000 IU	Olfactory function (Sniffin' Sticks)	Intranasal vitamin A could potentially be useful for treatment of postinfectious olfactory loss but more robust data is needed.
Kopala et al[32]	1995	3	Anorexia Nervosa	Cohort	(n=77) participants (27 Anorexia Nervosa patients.)	Olfactory function (UPSIT)	UPSIT scores are normal for anorexia nervosa patients. Transient metabolic or nutritional disturbances are unlikely to be responsible for long term olfactory dysfunction.
Dinc et al[33]	2016	3	Iron deficiency anemia (IDA)	Cohort	(n=100) participants (50 Iron deficiency anemia (IDA) patients.)	Olfactory function (Sniffin' Sticks)	Olfactory function decreases in IDA patients.
Hansen et al[34]	2017	4	Iron deficiency anemia (IDA)	Case Series	(n=3) patients with IDA	Olfactory craving	IDA is cause of

						symptoms (Self reporting)	Desiderosmia that is an olfactory craving phenomenon and this phenomenon is treated with clasical IDA treatment: iron.
Derin et al[35]	2016	2	Vitamin B 12 deficiency	Double-blind randomized, 375placebo-controlled clinical trial	(n=73) patients (39 patients with low level vitamin B 12)	Olfactory function (Sniffin' Sticks)	Olfactory dysfunction may be present in patients with vitamin B12 deficiency.
Haglin et al[37]	2016	3	Vitamin B intake, parkinson's disease (PD)	Cohort	(n=420) participants (84 cases, parkinson's disease.)	Olfactory function (Brief Smell Identification Test)	Low thiamin (vitamin B1) and folate in the diet 2-8 years prior in PD patients related with olfactory dysfunction at the time of PD diagnosis.
Heilmann et al[38]	2004	3	Posttraumatic, Postinfectious olfactory loss, vitamin B and corticosteroid treatment	Cohort	(n=192) patients (72 cases, postinfectious olfactory loss)	Olfactory function (Sniffin' Sticks)	Systemic vitamin B treatment is not effective after 2 months, but if vitamin B given for full 6 months, treatment may be useful for smell function,

							although there was no control group and no time restriction controlling for spontaneous resolution.
Selhub et al[39]	2000	4	Vitamin B, neurocognitive function	Review	Review Articles	Vitamin B and homocysteine relationship with neurocognitive function.	Cognitive dysfunction may be related with low vitamin B level and high homocysteine concentrations

Investigating and treating vitamin and mineral deficiency in patients with related OD
Aggregate Grade of Evidence: -C (Level 2: 3 studies; Level 3: 4 studies; Level 4: 7 studies)

Benefit: Detecting underlying deficiencies of Vitamin A, serum iron and vitamin B12, and then replacing them, may help with OD as well as other symptoms related to the underlying deficit.

Harm: Known potential side effects and adverse events associated with vitamin supplementation.
Cost: Cost of vitamin level testing and supplementation.
Benefits-Harm assessment: Vitamin B12 treatment can eliminate mild cognitive impairment, iron replacement treatment can treat iron deficiency anemia, and Vitamin A replacement can help individuals with liver disorders. OD related to these underlying disorders can also then improve. Only if taken without medical supervision is the potential harm of vitamin toxicity a potential issue.
Policy level: Evaluating and treating patients with olfactory disorders related to suspected or known iron, Vitamin A, Vitamin B12, or other related vitamins and mineral deficiencies, is **recommended**.
Intervention: Laboratory tests, including serum iron, vitamin B12, vitamin A and potentially other related vitamin and mineral levels should be considered in individuals with suspected deficiencies and related OD.

SECTION: XI. Management

F. If no underlying disease state to correct:

1. Treatment with corticosteroids

The evidence for steroids, both topical and systemic, as treatment for non-sinonasal disease related olfactory loss is limited, as recently highlighted in a systematic review.[1] While excluding rhinosinusitis and rhinitis, the causes of these olfactory losses remain heterogeneous and include post-infectious, post-traumatic, and idiopathic etiologies. Baseline severity of olfactory dysfunction is varied amongst subjects and studies ranging from mild hyposmia to functional anosmia, and differing olfactory measurements make it difficult to directly compare studies.

Five studies investigated the use of topical steroids in non-sinonasal disease olfactory loss (**Table IX-25**). In three uncontrolled cohort studies (level 4), 20% (23/117 subjects) demonstrated clinically significant improvement in olfactory measures using topical steroid sprays.[2–4] However, a small RCT found no olfactory benefit from the addition of topical steroid sprays (fluticasone) in subjects who were previously responsive to oral steroids.[5] Currently, there is no strong data supporting the use of topical steroid sprays. However, one RCT demonstrated efficacy with the use of topical steroid irrigations in the treatment of non-sinonasal inflammatory related olfactory loss. Subjects using twice daily budesonide nasal rinses along with olfactory training (OT) were more likely to achieve clinically significant improvement compared to saline rinses with OT (43.9% vs 26.9%, p=0.039).[6] Additional RCT studies would be useful to corroborate this finding.

There is a paucity of studies evaluating the optimal head position for topical steroid delivery to the olfactory cleft, with most utilizing cadaveric models (**Table IX-26**). Two studies reported successful irrigation delivery to the olfactory epithelium using the head-over-sink position.[7,8] Even in maximal post-surgical conditions (modified Lothrop), topical rinses had superior olfactory cleft penetration compared to topical sprays.[8] Other head positions (head-tilted forward, vertex-to-floor, neutral position, head reclined, and lateral head low) have demonstrated variable success in topical delivery.[7–15] Middle turbinate resection failed to improve delivery of irrigation to the olfactory mucosa.[16] Thus, the volume of rinses appears to be important in accessing the olfactory mucosa and may explain why nasal steroid rinses but not sprays are beneficial in treatment of non-sinonasal disease olfactory dysfunction.

Meanwhile, the use of systemic steroids alone in non-sinonasal disease related anosmia remains equivocal with only weak evidence favoring its use (**Tables IX-27,28**). The most commonly used corticosteroid was oral prednisolone with a starting dose of 30-60mg per day and a 2-week taper. Five cohort studies with a total of 553 subjects demonstrated that 16.4%-49.6% subjects treated with systemic steroids had a significant improvement in olfaction threshold measurements[2,17–20] with 2 studies demonstrating clinically meaningful improvements of threshold-discrimination-identification in 12-29% of subjects.[2,20] Systemic steroids were not beneficial in a small retrospective case series of subjects who were non-respondent to topical therapy[21] and a RCT of subjects with post-traumatic olfactory dysfunction though this study may have been underpowered.[22] Systemic steroids appear to have an additive benefit when used in conjunction with topical steroids.[23] Three retrospective studies totaling 554 subjects reported improved olfactory function in patients receiving systemic and topical steroids compared to topical steroid sprays alone.[24–26] For most of these studies, inclusion of patients early (<6months) into the course of olfactory loss may allow for spontaneous recovery to confound their results. Notably no adverse effects were reported in any these studies, though the potential risks of systemic corticosteroids given even in short bursts, have been well documented.[27]

Overall, the literature supporting the use of steroids in non-sinonasal inflammatory etiologies of anosmia is limited with few RCTs. Topical steroid sprays are not recommended given their general lack of efficacy and limited delivery to the olfactory cleft. Topical steroid rinses are recommended, with one high level of evidence study showing benefit with a minimal side effect profile. Oral steroids remain an option with only weak evidence supporting their efficacy, against which treatment risks must be considered and balanced. With both therapeutics, additional largescale RCTs are required to further elucidate their efficacy, dosage, and timing in the treatment of non-sinonasal disease olfactory dysfunction.

Table IX.25. Systematic review of topical steroid treatments for OD

Author	Year	LOE	Study Design	Study Groups	Clinical End-point	Results

Yan, et al.[1]	2019	2	Systematic Evidence Based Review with Recommendations (EBRR)	Patients with olfactory loss treated with systemic steroids, topical steroids or both.	Studies included only objective psychophysical test confirmation of smell loss: (UPSIT, Sniffin' Sticks, etc.)	Topical steroid sprays are NOT effective in treating olfactory dysfunction from non-sinonasal inflammatory etiologies, but topical steroid irrigations ARE effective in treating this patient population.
Blomqvist et al[5]	2003	2	Randomized Controlled Trial, double-blinded	Population: 30 URI or idiopathic Severity of Smell loss: mixed, details n/a Duration of loss: up to 6.6 yrs Treatment: All pts pre-treated with 10d oral prednisolone 40mg qd taper + 10d fluticasone spray: only improved pts included 1. 20 pts: topical fluticasone spray: 2 spray BID (200ug qd) x 6 mo. 2. 10 pts: placebo spray 3. 10 pts: no treatment	Follow-up: 6 mo. Olfactory measurement: CCRC	1. No statistically significant difference in olfactory thresholds or scored sense of smell amongst the three groups. 2. No treatment group had decrease in olfactory threshold at 2 months
Fleiner et al[3]	2011	4	Prospective Cohort	Population: 13 URI or idiopathic Severity of Smell loss: mixed, details n/a Duration of loss: 2-120 mo. (median 28 mo.)	Follow-up: 4 wks Olfactory measurement: Sniffin' Sticks	Median improvement TDI score 2 pts, 2 of 13 pts (15.4%) had clinically relevant

				Treatment: Beclomethasone spray BID x 4 wks		change in TDI score (6 pts)
Fleiner et al[4]	2012	4	Retrospective Case series	Population: 31 URI, Post-traumatic, Idiopathic Severity of Smell loss: 13/31 (42%) hyposmic, 18/31 (58%) anosmic Duration of loss: 10.5-36 mo. (median 21 mo.) Treatment: 1. 18 pts olfactory training only 2. 13 pts treated with topical steroid (dose n/a)	Follow-up: 8 mo. Olfactory measurement: Sniffin' Sticks	1. Steroid + olfactory training mean TDI improved 6.83pts ($p<0.001$) vs olfactory training mean TDI improved 2.20 pts. 2. 5 of 13 pts (38.4%) had clinically significant improvement (≥ 6pts) at 8 months with topical steroids + olfactory training
Nguyen and Patel[6]	2018	2	Randomized Controlled Trial	Population: 66 tx / 67 controls. All non-CRS or rhinitis etiologies, Duration of loss: >6 mo. Severity of Smell loss: n/a Treatment1. Budesonide 0.5mg/2ml BID nasal rinses +olfactory training (OT) 2. Saline rinses +OT	Follow-up: 6 mo. Olfactory measurement: UPSIT	1. 43.9% significant improvement in budesonide rinses +OT vs. 26.9% improvement in saline +OT ($p=0.039$). 2. Younger age and shorter duration of olfactory loss were significant predictors of improvement ($p<0.0001$ for both).
Stenner et al[2]	2008	4	Retrospective Case series	Population: 73 l non-CRS etiologies	Follow-up: 12 wks	1. Oral steroids improved mean TDI

				Severity of Smell loss: mixed, details n/a Duration of loss: 2-520 mo. (mean 55 mo.) Treatment: All pts tx with beclomethasone 15mg qd x 20d taper. After 12 wks, pts tx topical budesonide 1.5mg BID OR budesonide + neomycin 7.5mg qd Follow-up: 12 wks Olfactory measurement: Sniffin' Sticks	Olfactory measurement: Sniffin' Sticks	from 15.5 to 18.7 ($p<0.001$), 27% had clinically meaningful improvement of TDI by at least 6 pts 2. Topical treatment did not further improve TDI overall (18.7 to 18.9pts), but 12% had clinically meaningful improvement TDI. 3. No change with topical antibiotics
LOE = level of evidence, CCCRC = Connecticut Chemosensory Clinical Research Center test, UPSIT = University of Pennsylvania Smell Identification Test, TDI = threshold-discrimination-identification score						

Table IX.26. Systematic review on head position for topical medication to reach olfactory mucosa

Author	Year	LOE	Study Design	Study groups	Clinical End-point	Results
Lam et al[7]	2013	5	Cadaveric study	Population: 8 cadaveric heads, total of 15 nasal sides received methylene blue solution using spray device and irrigation squeeze bottle.	Assessed approximate surface area stained and quantified surface delivery of methylene blue. Head position: Spray: Forward-tilted position	Irrigations delivered greater surface area and intensity of staining compared to sprays ($p<0.05$)

					with sprays directed away from septum. Irrigation: Head-over-sink position.	
Beule et al[8]	2013	5	Cadaveric study	Population: 15 cadaveric heads s/p endoscopic modified Lothrop procedure and complete sphenoethmoidectomy.	Assessed nasal spray and squeeze bottle (50ml, 100ml, and 200ml). Head position: bending over the sink vs vertex to floor.	Nasal irrigation 200 ml stained surface of olfactory region more than 100 ml, 50 ml and spray. Bending over the sink stained the olfactory epithelium better than vertex to the floor.
Scheibe et al[9]	2008	4	Observational	Population: 15 healthy volunteers	Assessed the distribution of topical pipette (head reclined as much as possible), nasal spray, and system producing squirts.	Squirt reached olfactory cleft in 73% of participants ($p<0.001$)
Herranz Gonzalez-Botas and Seara[10]	2012	4	Observational	Population: 16 healthy volunteers.	Assessed distribution of topical dye in neutral position with radial hole inhaler.	No nasal gel was found at the olfactory cleft.
Cannady et al[11]	2005	4	Observational	Population: 6 patients post-FESS patients with a total of 11 sides.	Compared delivery of spray in vertex to floor position for one and 5 minutes with atomizer in upright position.	Vertex to floor position with 5 minutes had a significant increase of spray delivery to olfactory cleft ($p=0.012$).

Rudman et al[12]	2011	4	Observational	Population: 9 volunteers.	Detected radiopaque contrast solution in spray versus drops. Drops were instilled in the "vertex-to-floor position".	The olfactory cleft was not penetrated by either spray or drops >50% of the time and there was no significant difference between the two methods (p>0.05)
Manes et al[13]	2011	5	Cadaveric study	Population: 5 cadavers.	Investigated the distribution of aerosol delivered via powered nasal nebulizer in unoperated nose, post-functional endoscopic sinus surgery, and post-functional endoscopic sinus surgery with endoscopic modified Lothrop procedure. Head position: head tilted 45 degrees downward and the chamber at a 30 degree angle to the face.	No significant difference in delivery to the olfactory cleft (p=0.885).
Raghavan and Logan[14]	2000	5	Cadaveric study	Observed distribution of nasal drops in cadaveric specimens in head back, head down and forward, lateral head low, and lying head back position.	n/a	Head down and forward position demonstrated distribution of drops to

						olfactory cleft.
Mori et al[15]	2016	4	Observational	Population: 13 healthy volunteers.	Applied drops while lying on side with head tilted and the chin turned upward.	Nasal drops reached the olfactory cleft in 96% and 75% of decongested patients and patients without decongestion, respectively.
Kidwai et al[16]	2017	5	Cadaveric study	Population: 4 cadaver heads.	240 ml irrigation bottle in head over sink position in unoperated and post-middle turbinate resection.	No significant difference in the delivery of irrigation to olfactory cleft before and after middle turbinate resection (p=0.340)

TableIX-27. Systematic review of systemic steroid treatments

Author	Year	LOE	Study Design	Study Groups	Clinical End-point	Results
Yan, et al.[1]	2019	2	Systematic Evidence Based Review with Recommendations (EBRR)	Patients with olfactory loss treated with systemic steroids, topical steroids or both.	Studies included only objective psychophysical test confirmation of smell loss: (UPSIT, Sniffin' Sticks, etc.)	There is weak lower level evidence only to support use of systemic steroids to treat non-sinonasal inflammatory etiologies of olfactory dysfunction, and their use should be balanced against their known potential side effects and adverse events.
Fujii et al[17]	2002	4	Prospective, single arm trial	Population: 27 Trauma patients Severity of Smell loss: 61% (16) anosmia, 19% (5) severe hyposmia, 11% (3) moderate hyposmia, 8% (2) mild hyposmia	Follow-up: 4 mo Olfactory measurement: T&T, Alinamin test	1. 35.3% improvement in recognition and 23.5% improvement in detection thresholds by T&T 2. Patients treated <2mo after trauma had higher rates of improved recognition & detection

				Duration of loss: <2mo - >120mo Treatment: Dexamethasone injection 4mg/0.5ml septal mucosa every 2 weeks x 8		
Fukazawa et al[18]	2005	4	Prospective, single arm trial	Population: 133 URI patients Severity of Smell Loss: ~70% severe hyposmia / anosmia Duration of loss: n/a Treatment: Dexamethasone or betamethasone (5mg) injection q2 wks x 8-10 times	Follow-up: n/a Olfactory measurement: T&T, VAS	49.6% improvement in olfaction threshold recognition by at least 1 pt by T&T. VAS improved from 10.2 to 39.5
Ikeda et al[21]	1995	4	Retrospective case series	Population: 9 URI patients Duration of loss: 1-15mo Treatment: Failed topical Beclomethasone, Oral prednisolone 40-60mg x 10 - 14 days with taper	Follow-up: n/a Olfactory measurement: T&T	No statistically significant improvement in olfaction detection or recognition by T&T
Jiang et al[19]	2010	4	Prospective, single arm trial	Population: 116 Trauma patients Severity of Smell loss: All anosmic Duration of loss: 1-264mo Treatment: Prednisolone x 15 days starting at 60 mg with taper q3 days	Follow-up: 3 - 21.5 mo (mean 5.5 mo) Olfactory measurement: PEA threshold test	1. 16.4% (19 / 116 pts) PEA threshold improved 2. Younger patients more likely to improve in olfaction (p= 0.033) 3. No difference in interval of olfactory loss b/n pts who showed improvement and those who didn't (p=0.88)
Jiang et al[22]	2015	2 (<80% follow-up)	Randomized Controlled Trial	Population: Trauma, 34 treat / 37 controls Severity of Smell loss: All anosmic Duration of loss: 0.5 - 180 months Treatment: 1. prednisolone (1mg/kg/day taper	Follow-up: 3 - 15.5 mo (mean 5.6 mo) Olfactory measurement: PEA threshold test	1. 4 of 34 (11.8%) improved with steroid vs. 1 of 37 improved (2.7%) in no treatment group, not statistically significant 2. Younger patients more likely to improve (p =0.007)

				for 2 weeks) 2. no treatment 3. Zinc 4. zinc with prednisolone		
Schriever et al[20]	2012	4	Retrospective case series	Population: 204 total: Idiopathic (157), URI (27), Trauma and Other (20) Severity of Smell loss: Mixed Duration of loss: mean 67 +/- 76 months Treatment: 40mg methylprednisolone x 14 days with taper	Follow-up: 2 visits Olfactory measurement: Sniffin' Sticks	1. All etiologies 26.6% clinically significant improvement (≥ 6 TDI pts), mean TDI improvement 3.25 pts 2. Idiopathic etiology: 12.1% clinically significant, mean TDI improvement 1.0 pt. 3. URI etiology: 29.6% clinically significant improvement, mean TDI improvement 4.5 pts
Stenner et al#[2]	2008	4	Retrospective Case series	Population: 73 All non-CRS etiologies Severity of Smell loss: mixed, details n/a Duration of loss: 2-520 mo. (mean 55 mo.) Treatment: All pts tx with oral beclomethasone 15mg qd x 20d taper. After 12 wks, pts tx topical budesonide 1.5mg BID OR budesonide + neomycin 7.5mg qd Follow-up: 20 d (after oral steroids only) Olfactory measurement: Sniffin' Sticks	Follow-up: 20 d (after oral steroids only) Olfactory measurement: Sniffin' Sticks	1. Oral steroids improved mean TDI from 15.5 to 18.7 ($p<0.001$), 27% had clinically meaningful improvement (≥ 6 TDI pts) 2. Topical treatment did not further improve TDI overall 18.7 to 18.9pts, but 12% had clinically meaningful improvement TDI. No change with topical antibiotics

*Also included in Table 1, studies included both topical and systemic steroid use.
#Also included in Table 1, patients were treated first with systemic steroids then topical steroids.
LOE = level of evidence, T&T = Toyota & Takagi olfactometer, VAS = visual analogue scale, PEA = phenyl ethyl alcohol, TDI = threshold-discrimination-identification score

Table IX-28. Systematic review of systemic steroid with or versus topical steroid treatment

Author	Year	LOE	Study Design	Study design	Clinical End-point	Results
Heilmann et al[26]	2004	4	Retrospective Case Series	Population: 55 oral / 37 topical URI or Idiopathic Duration of loss: 3-360 mo. Treatment: 1. Oral prednisolone 40mg x 21d taper 2. Mometasone spray daily x 1-3 mo.	Follow-up: 21-330 d Olfactory measurement: Sniffin' Sticks	1. All TDI improved w systematic steroids ($p<0.0001$), both URI ($p=0.05$) and idiopathic ($p=0.008$) 2. Mometasone spray didn't improve olfactory function. 3. For both topical and systemic steroids, no difference in olfactory improvement based on patient age, duration of disease, gender, parosmia
Ikeda et al[25]	1995	4	Retrospective case series	Population: 5 oral / 12 topical Trauma Duration of loss: Improved pts mean: 72.3 mo., Unimproved pts: 22.4 mo. (no sig diff) Treatment: 1. Oral prednisolone 30-60mg x 10-14d taper 2. Topical betamethasone BID	Follow-up: 6-12 mo. Olfactory measurement: T&T, intravenous olfaction test (thiamine propyl)	3 of 5 pts improved from oral steroid in T&T and IV testing, 1 of 12 improved from topical steroid treatment
Kim et al[24]	2017	4	Retrospective Case series	Population: 374 URI, Trauma, xerostomia, Congenital or Idiopathic Duration of loss: mean 78.4 mo. Treatment: 1. Oral prednisolone 40 mg x 14d with taper by 5 mg qd 2. Topical Nasonex, 2 sprays in each nostril (total, 200 mg/d) 3. Systemic + Topical	Follow-up: 1 mo. Olfactory measurement: CCCRC CCSIT, subjective "recovery" v "no recovery"	Systemic or systemic + topical is better than topical alone in smell threshold and identification and recovery ($p < 0.001$). No difference between systemic vs. systemic + topical treatment groups ($p=0.978$)
Seo et al[23]	2009	3	Randomized, non-blinded, parallel group	Population: 28 one arm / 43 second arm URI Duration of loss: mean 3.4 mo Treatment: All on mometasone nasal spray 1. Prednisolone x 2 wks tapering from 30mg daily 2. Prednisolone x 2 wks + G Biloba x 4 wks.	Follow-up: 4 wks Olfactory measurement: BTT, CCSIT	1. With prednisolone + mometasone spray, 32% had improved BTT score (≥3 pts), mean 1.4 pts and 14% had improved CCSIT (≥ 3pts) mean 0.9 pts 2. Both BTT and CCSIT improved $p< 0.001$ 3. no statistically significant difference b/w steroids alone and steroids + g. biloba

LOE = level of evidence, TDI = threshold-discrimination-identification score, T&T = Toyota & Takagi olfactometer, CCCRC = Connecticut Chemosensory Clinical Research Center test, CCSIT = Cross-Cultural Smell Identification Test; aka Brief Smell Identification Test (B-SIT), BTT = butanol threshold test

The use of steroids to treat OD not related to underlying inflammatory sinonasal disease.
Aggregate Grade of Evidence: C (Level 2 studies:4, Level 3 studies: 1, Level 4 studies: 17, Level 5 studies: 5)
Benefit: Use of budesonide irrigations and systemic steroids may improve anosmia secondary to non-sinonasal inflammatory etiologies of OD.
Harm: No adverse effects have been reported in these particular studies with systemic steroids, however side effects and potential adverse events associated with this therapy are well known and must be considered on a case-by-case basis.
Topical steroids have a well-established and well-tolerated low side effect profile.
Cost: Cost of steroid treatment options.
Benefits-Harm assessment: There are no reported adverse effects with use of topical or systemic steroids for non-sinonasal disease related anosmia. However, side effects of systemic steroids are well known and must be considered on case-by-case basis.
Value Judgments: Steroid irrigations and systemic steroids may help improve non-sinonasal inflammatory related anosmia.
Policy level: Systemic steroids are an **option** for treatment of OD. Topical steroid irrigation is **recommended** in patients with OD. There is **no recommendation** for use of topical corticosteroid sprays or drops. There is **no recommendation** for optimal head position.
Intervention: The use of steroid irrigations, and potentially systemic steroids, should be considered for treatment of patients with OD in an informed discussion between the patient and the provider.

SECTION: XI. Management

F. If no underlying disease state to correct:

2. Olfactory training

Olfactory training (OT) is performed by smelling specific sets of odors twice daily for an extended period of time. Hummel et al. in a landmark study first reported benefit from olfactory training in patients with olfactory loss where patients smelled 4 odors twice daily for 12 weeks. The odors selected in this initial study were based on the odor prism and were initially chosen somewhat arbitrarily, but do represent different categories of smell. This method is now considered classic olfactory training (COT) – including smells from categories of floral (rose), fruity (lemon), resinous (eucalyptus) and aromatic (clove) groups.[1] There has been a significant amount of interest and research into this treatment modality since that initial study - this review identified 22 studies examining olfactory training for olfactory loss (3 meta-analyses, 2 systematic reviews, 4

randomized controlled trials, 4 prospective randomized trials, 2 prospective pseudo-randomized studies, and 7 prospective cohort studies – **Table IX-29**).

Benefit with olfactory training has been reported in patients with post-traumatic (PTOD), post-infectious (PIOD) and idiopathic olfactory dysfunction (IOD), as well as with olfactory dysfunction related to Parkinson's disease and aging. While all studies report some benefit for OT regardless of etiology, the benefit appears to be greatest for patients with PIOD. Liu et al. performed a retrospective pooled analysis of 8 previously published studies. They found an adjusted odds ratio of 0.29 for PTOD and 0.18 for IOD versus PIOD.[2] Patients with PIOD have an odds ratio of 2.77 of achieving a minimum clinically important difference (MCID) on olfactory testing versus control.[3] A shorter duration of olfactory loss has also been associated with greater recovery with OT in several studies.[4–6] Haehner et al[7] found in a prospective cohort study with COT for 12 weeks in patients with Parkinson's Disease an improvement on TDI and an improvement on threshold for the 4 scents used for training. Lastly, Lamira et al[8] found that OT in adults with age-related olfactory loss (mean age 66) had a clinically significant improvement in olfaction in 44% of patients that completed the study, but had a dropout rate of 45%. Two systematic reviews concluded that improvement is primarily in the discrimination and identification realms.[9,10]

Most studies have performed OT using 4 different odors, with the majority using the COT technique, but the odors used do not appear to have a significant effect on outcome.[1,3] Patel et al[11] reported that OT with non-standardized concentrations of commercially available essential oils was as effective as prior studies using pure odorants, achieving an MCID in 32% of patients (vs. 10% of controls). Altundag et al[12] noted incremental improvement in olfactory recovery in patients with PIOD when using 3 different sets of 4 odors for training versus COT for 36 weeks. Conversely, Saatci et al[13] compared the MOT method to an olfactory training ball containing the same odors as in COT but found greater improvement with the olfactory training ball. Oleszkiewicz et al[14] used 3 different training regimens (COT, 4 scent mixtures and three sets of 4 odors) in patients with IOD or PIOD. All groups exhibited an improvement in TDI scores, but there was no difference between groups. Jiang et al[15] compared the use of a single scent (phenyl ethyl alcohol - PEA) versus COT in PTOD for 6 months and found no clinically

significant difference in rates of olfactory identification between groups, and that both groups showed a similar improvement in PEA thresholds. Poletti et al[16] found little difference in olfactory recovery in patients with both PTOD and PIOD when training was performed with either light-weight or heavy-weight molecules. Langdon et al[17] used 6 odors (anise, lemon, rose, vinegar, smoke and eucalyptus) for OT in patients with PTOD and noted a significant improvement in n-butanol threshold. Lastly, Qiao et al[18] found an equivalent recovery in patients with PIOD when COT was compared to using household scents (balm, vinegar, alcohol and rose perfume) instead, with 41% improving above the TDI MCID threshold in both groups.

While several studies used an OT duration of 12-16 weeks, other studies have found that a prolonged duration of OT may have increased incremental benefit. Konstantinidis et al[19] demonstrated rapid improvement in both short and long-term training groups in the first 4 months, with a modest further improvement over the following 9 months for those that continued to train. Those in the short-term group maintained their benefit without further training. At the end of the study, 71% in the long-term group met MCID thresholds for TDI, versus 58% for the short-term training group and 37% in the control group. Adherence to therapy has been shown to be a challenge.[3] Fornazieri et al[20] found an adherence rate of 88% after 3 months and 56% after 6 months. By making OT more convenient, Saatci et al[13] demonstrated improved adherence with an olfactory training ball (56% vs. 30%) over 12 weeks.

Overall, all 22 studies have reported some improvement with olfactory training. A wide variety of odors have been reported to be effective and are most effective with good adherence to therapy for a longer duration of time. The degree of recovery in all studies is modest, just meeting the threshold for a MCID difference. Only 4 studies had randomized controls and blinding patients to therapy remains a challenge.

Table IX-29. The Use of Olfactory Training to Treat Olfactory Dysfunction

Study	Year	LOE (1-5)	**Study design**	**Study Groups**	**Clinical End-point**	**Conclusion**
Kattar et al[3]	2020	1	Systematic review and meta-analysis	OT for PIOD. 16 studies included. 4 in meta-analysis.	Sniffin' Sticks	All studies reported clinically significant results after OT. OT had OR of 2.77 of achieving MCID vs. control.
Sorokowska et al[9]	2017	1	Systematic review and meta-analysis	13 studies.	Sniffin' Sticks	Strong significant relationship with OT and discrimination and identification, and overall TDI score improvement. PIOD has the strongest relationship with improvement.
Pekala et al[10]	2016	1	Systematic review and meta-analysis	10 studies. 3 for meta-analysis.	Olfactory improvement using psychophysical tests	OT improves TDI (3.77 mean difference). Discrimination and Identification improve, but not Threshold. Odds ratio of MCID 2.75.
Hura et al[5]	2020	1	Systematic review (EBRR) for PIOD	10 studies for OT	Effectiveness of OT, medical therapy	OT was effective in all 10 identified studies.
Addison and Philpott[21]	2018	1	Systematic review	1 meta-analysis, 6 studies.	Effectiveness of OT, medical therapy	OT is effective for improving olfaction in olfactory loss.

Langdon et al[17]	2018	2	Prospective, randomized, controlled trial	42 patients with PTOD. 1)OT with 6 odors for 12w (21) 2)Controls (21)	1)UPSIT 2) BAST-24 3) n-BTt 4)VAS	No significant difference in UPSIT, BAST-24, VAS. 26% vs. 5% met MCID for nBTt at 12 weeks, but not sustained at 24 weeks.
Patel et al[11]	2017	2	Prospective, randomized controlled trial	43 patients with PIOD or IOD for >12m. 1)OT with 4 essential oils for 26w (19) 2)Controls (16)	UPSIT	32% in OT group (vs. 13% in control group) had >10% improvement on UPSIT.
Damm et al[6]	2014	2	Prospective, blinded randomized controlled multi-center trial	171 patients with PIOD for 2-24 months. 1) high concentration COT (70) 2) low concentration COT (74). Cross-over at 16w	1)Sniffin' Sticks 2) 5-point subjective ranking scale	TDI improved by 3.0 in high vs. 2.8 in low at 16 weeks. 26% vs. 15% met MCID. 53% vs. 34% subjective improvement at 32 weeks.
Jiang et al[22]	2017	2	Prospective, randomized controlled trial	83 patients with PTOD. OT with 1) PEA (42) 2) mineral oil (39) for 3m	1)PEA threshold 2)UPSIT-TC 3)MRI olfactory bulb volume	PEA threshold - 24% improved in OT group vs. 5% in control. No difference in UPSIT or OB volume.
Qiao et al[18]	2020	2	Prospective, randomized trial	125 patients with PIOD. 1) COT (60) 2) household OT (65) (balm, vinegar, alcohol, rose perfume) for 24w	Sniffin' Sticks	TDI improved by 5.7 and 6.6 in groups, with MCID improvement in 41% in both at 6 months. D and I also improved in both, but no change in T.

Saatci et al[13]	2020	2	Prospective, randomized trial	60 patients with PIOD. 1) OT training ball with 4 scents (30) 2) MOT (30) (Altundag) for 12w	1)Sniffin' Sticks 2)Adherence to OT	TDI improvement greater in training ball group (6 vs 3.7). Discrimination also had greater improvement. Adherence to therapy 63% vs. 30%.
Jiang et al[15]	2019	2	Prospective randomized trial	111 patients with PTOD. 1) COT (45) 2) PEA alone (45) for 6m	1)UPSIT-TC 2)PEA threshold 3) MRI olfactory bulb volume	Both groups had improvement in PEA threshold. UPSIT improved in PEA group (+1.6), not in COT. MRI not different between groups.
Oleszkiewicz et al[14]	2018	2	Prospective, randomized trial	108 patients with PIOD or IOD. 1) 4 odors (30) 2) 4 odor mixtures (23) 3) 3 x 4 odors, changing every 2m (20). OT done for 4-12m	Sniffin' Sticks	No effect of training regimen on recovery. Overall TDI improved for all groups. T and I improved, but not D.
Poletti et al[16]	2017	3	Prospective, pseudo-randomized, single blinded	96 patients with PIOD (70) and PTOD (26). 1) HWM (48) 2)LWM (48) OT for 5m.	1)Sniffin' Sticks 2) PEA threshold	PIOD MCID improvement 3x PTOD (45% vs 16%). Only difference between HWM and LWM found for threshold in PIOD. Others NS.
Konstantinidis et al[19]	2016	3	Prospective, partially randomized, controlled study	111 patients with PIOD. 1) COT for 16w (36) 2) COT for 56 w (n=34) 3) control (41)	1) Sniffin' Sticks 2) Subjective olfactory function	Improvement in TDI of 9.1 for 16 weeks, 11.4 for 56 weeks, 5.3 for control. (58% vs. 71% vs. 37% meeting MCID). Identification only significant sub-group

Choi et al[23]	2021	3	Prospective cohort study	104 patients with PIOD. 1) OT with rose, lemon, cinnamon, orange, peach for 12w (40) 2) control (64)	1) Korean Version Sniffin' Sticks 2) VAS	Improvement in TDI of 4.6 vs. 2.7 for control. Threshold improved by 2.1 vs 0.7 in control, Identification improved by 1.6 vs. 0.8 in control. No difference in Discrimination.
Gellrich et al[24]	2018	3	Prospective cohort study	30 patients with PIOD. 31 normosmic controls. Classic OT for 12w.	1) Sniffin' Sticks 2)Gray matter (GM) volume on MRI	TDI improved by 5.5 with OT. Increased volume of GM in hippocampus, thalamus and cerebellum after OT.
Hummel et al[25]	2018	3	Prospective cohort study	50 patients with PIOD or idiopathic loss. 1) COT for 16-24w (23) 2) control (27).	1)Sniffin' Sticks 2)EOG	No improvement on overall composite TDI. 35% met MCID improvement. EOG response to PEA and H2S improved with OT.
Altundag et al[12]	2015	3	Prospective cohort study	85 patients with PIOD 1) 3 sets of 4 odors (37) 2) 4 odors (33) 3) control (15) for 36w	1) Sniffin' Sticks 2) VAS	Changing odors improved recovery vs standard OT. 56% met MCID vs 46% vs. none in control. (TDI 8.2 vs. 6.1 vs. 1.7) Improvement was in D and I domains. VAS 5.6 vs. 5.2 vs. 2.8
Konstantinidis et al[4]	2013	3	prospective cohort study	119 patients with PTOD (38) and PIOD (81) 1)COT with 4 odors (72) 2)Controls (47) for 16w	1)Sniffin' Sticks 2) Subjective olfaction	Improvement seen in both groups vs control, more in PIOL. Improvement in D and I domains. (TDI 6.25 vs. 1.5 PIOL, 5.1 vs 1.2 PTOL). Subjective ratings also improved in OT groups.

Haehner et al[7]	2013	3	Prospective cohort study	70 patients with PD. 1)COT (35) 2)Controls (35) for 12w	1)Sniffin' Sticks 2)Thresholds for other odors	TDI improved by 2.4 for OT vs. -0.6 for controls. Thresholds for all 4 odors improved and discrimination also improved in OT group.
Hummel et al[1]	2009	3	Prospective cohort study	56 patients with PIOD (35), PTOD (7) or IOD (14). 1)COT (40) 2)Controls (16) for 12 w	1)Sniffin' Sticks 2) PEA odor thresholds	Significant difference in OT TDI vs. control. Thresholds improved, but not D or I scores. 28% in OT group met MCID vs. 6% in control

PIOD = Post-infectious olfactory dysfunction; PTOD = post-traumatic olfactory dysfunction; IOD = idiopathic olfactory dysfunction; OT = olfactory training; PD = Parkinson's Disease; TDI = threshold, discrimination and identification scores on Sniffin' Sticks; MCID = minimal clinically important difference; HWM = Heavy Weight Molecules, >150g/mol; LWM = Light Weight Molecules, <150g/mol; EOG - electro-olfactogram; UPSIT = University of Pennsylvania Smell Identification Test; BAST-24 = Barcelona Smell Test 24; n-BTt = n-Butanol Threshold Test; PEA = phenyl ethyl alcohol.

Olfactory Training for Patients with OD

Aggregate Level of Evidence**:** B (5 Level 1, 8 Level 2, 9 Level 3).

Benefit: Modest improvement in objective olfactory measures (UPSIT score, TDI score, Discrimination and Identification) and subjective perception of olfaction

Harm: Low: Expense of odorants, inconvenience of daily olfactory training

Cost: Ranges from minimal to high. Minimal cost for household items to $40 USD for commercially available kits. Individual essential oils can cost as low as $1 per bottle to upwards of $150.

Benefits-Harm Assessment: Preponderance of benefit over harm given low risk potential and established improvement in clinical trials. Expectations for recovery should be tempered.

Value Judgments: As an adjunctive therapy, olfactory training can empower patients struggling with anosmia and provide some hope for olfactory recovery during a difficult adjustment period. Value is high.

Policy Level: Recommendation

Intervention: Olfactory training is recommended in conjunction with other treatments for olfactory loss and should be started as soon as olfactory loss is identified. Further investigation into odorants (number and type), duration, and frequency is warranted.

SECTION: XI. Management

F. If no underlying disease state to correct:

3. Intranasal sodium citrate

Sodium citrate, a solution licenced and used safely in other body cavities (e.g. stomach and bladder) is known to buffer calcium ions (Ca^{2+}) and reduce mucosal Ca^{2+}. Intranasally, sodium citrate is able to sequester calcium ions. This is thought to reduce free mucosal calcium with subsequent reduction in negative feedback and increasing sensitivity to odorants.

Recent systematic reviews have highlighted sodium citrate as a potential treatment modality in post-infectious olfactory dysfunction (PIOD)[1] and non-conductive olfactory disorders.[2] Four interventional studies have been identified – two prospective studies and two randomized controlled trials (RCTs). With the exception of the most recent study that focused on PIOD, the remainder had mixed etiology groups included. Two studies used patients as their own controls, with monorhinal application of citrate. No studies examined the effect of long-term therapy.

In 2016, Whitcroft et al[3] performed a prospective placebo-controlled trial of monorhinal treatment of sodium citrate versus sodium chloride for patients with olfactory loss (multiple aetiologies, n=57) and showed improved olfactory threshold and identification only in the PIOD cohort (n=7). In 2017, Philpott et al[4] compared a single application of 0.5 ml of 9% sodium citrate per nostril versus sterile water (n=55) in an RCT and showed statistically significant improvement in olfactory function using olfactory thresholds lasting between 30 and 120 minutes after application.[4] In the latter study, the response rate was 1 in 3 of the treatment group as compared to none in the control group. In a prospective observational study, the duration of effect subjectively reported by patients was 3 hours.[7] The subsequent study by Whitcroft et al[6] looking specifically at PIOD showed an effect on combined threshold and identification scores, but not separately.[6]

The method of application differed across the four studies. In the Dresden studies, sodium citrate was applied with an intranasal 'squirt device', with patients lying supine throughout, with their neck extended and head back over the edge of the examination bed (approximately 35-40° below the horizontal) for 30 to 60 seconds. In the RCT by Philpott et al, the sodium citrate was applied using a repurposed co-phenylcaine bottle and nasal applicator with the patients in an upright position. In the original study by Panagiotopoulos et al,[7] patients were instructed to self-

administer the sodium citrate using a 2.5 ml syringe in the 'head down and forwards' position and then to stay there for 1 minute.

In summary, sodium citrate has shown some potential, especially in patients with PIOD but further studies are needed to confirm benefit in a well-designed RCT with an appropriate placebo arm, outcome measures, and longer-term follow up. Duration of improvement after one application appears to be short-lived.

Table IX-30. Use of Sodium Citrate to Treat Olfactory Dysfunction

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Panagiotopoulos et al[7]	2005	3	Prospective observational study (n=31) 1ml of sodium citrate – citrate acid (3.5g/140ml, pH 7.4, osmolarity 298) to both nostrils	Unspecified (16%) Post-traumatic olfactory loss (PTOL) (3%) Nasal Surgery (23%) PIOD (58%)	1) 12-item odor identification test of the "Sniffin' Sticks" 2) Reported side-effects	1) Thirty patients (97%) improved by mean of 4 points, 74% had subjective improvement lasting 3 hours 2)Itching most common side effect
Whitcroft et al[3]	2016	2	RCT with patients acting as own control (n=57) 1ml of sodium citrate solution (3.5g/140ml, pH 7.4, osmolarity 298) to one side	PIOD (12%) PTOL (18%) Sinonasal disease (53%) Idiopathic olfactory loss (18%)	1) Monorhinal Sniffin' Sticks identification and threshold (PEA) 20-30 minutes post treatment 2) Reported side-effects	1) Only increase seen was in PIOD identification scores (mean 2.29 ± 1.89) 2) Nasal discharge most common side effect
Philpot et al[4]	2017	2	RCT comparing bilateral sodium citrate with placebo (n=55) 1ml of 9% sodium citrate	Idiopathic (36%) PTOL (16%) PIOD (47%)	1) Threshold improvement for PEA (rose) 2) Threshold improvement for pear,	1,2) 32% had threshold improvement for rose, pear, or methanol 3)Peak improvement seen at 47 minutes; duration 54 minutes 4)Rhinorrhea, sore throat reported

			solution; 0.5ml to each side of the nose.		vinegar, methanol 3) Time until best improvement 4) Reported side-effects The four threshold tests were used at 15-minute intervals over 2 hours to measure any fluctuations in response	
Whitcroft et al[5]	2017	3	Prospective, single blind study with patients acting as own control (n=49) 1ml of sodium citrate solution (3.5g/140ml, pH 7.4, osmolarity 298) to left nostril	PIOD only	Monorhinal Sniffin' Sticks identification and threshold (PEA) 20-30 minutes post treatment	No difference in threshold or identification scores post-treatment. Composite score statistically but not clinically significant (+0.9, p=0.04)

Use of Sodium Citrate to Treat Olfactory Dysfunction

Aggregate Grade of Evidence: B (Level 2: 2 studies; Level 3: 2 studies)

Benefit: May improve olfactory performance for short duration (up to 2-3 hours), but replication of this result has varied.

Harm: Local irritation of nasal and oropharyngeal mucosa – short-term side effects (up to 30 minutes after application)

Cost: May include the following:

Direct costs: 16 USD for 500g of sodium citrate will provide treatment for several months

Indirect costs: time for daily therapy; could perhaps be used 3 times per day in conjunction with mealtimes but further evidence is needed

Benefits-Harm assessment: Minimal risk of short-term side effects versus low cost and potential for improvements to be discussed between clinician and patient. Those with PIOD may be the best group to select. No data on long-term use to advise on any potential longer-term harm.

Value Judgments: Although the existing data provide promise for transient improvement, this treatment needs evidence around long-term benefits and delivery. If efficacy can be proven and replicated, it is a low cost, low-risk option to offer patients.

Policy level: Option
Intervention: Topical sodium citrate can be considered an **option** for patients presenting with PIOD for short term improvement. Clinicians may need to provide a delivery device such as a mucosal atomiser to apply the solution.

SECTION: IX. Management
F. If no underlying disease state to correct:
4. Vitamins and supplements
a. Omega3

Omega-3 long chain polyunsaturated fatty acids (LCPUFA) are integral to lipid metabolism and play an important role in diet and physiology. In addition, they are critical in normal brain function and structure, with additional anti-inflammatory and antioxidant properties. In animal models, rats fed a diet deficient in docosahexaenoic acid (DHA), an omega-3 fatty acid, made significantly more errors in a series of olfactory-cued tasks.[1] Furthermore, omega-3 supplementation has been suggested to be protective against other neurologic insults and degenerative processes, such as Alzheimer's or diabetic sensorimotor polyneuropathy, both known pathologies that are associated with olfactory dysfunction (OD), as noted in prior sections.[2,3] Finally, accelerated functional recovery after peripheral nerve injury was detected among mice transgenically over expressing omega-3 LCPUFAs.[4]

There is one prospective RCT examining olfactory function after endoscopic sellar and parasellar tumor resection with omega-3 supplementation.[5] The 46 patients randomized to1000 mg of omega-3 supplementation, twice a day, plus saline irrigation postoperatively had significantly less olfactory loss on the UPSIT at 3 and 6 months post-operatively compared to the 41 who performed saline irrigations alone. While the magnitude of the immediate postoperative olfactory defect was not quantified, this study provides evidence supporting the potential role of omega-3 LCPUFAs in the treatment of postoperative olfactory dysfunction. Future research is needed to characterize the role of omega-3 supplementation in other etiologies of olfactory loss. A population-based cohort of 667 Australians found that older adults with the highest consumption of nuts and fish, sources of omega-3 fatty acids, had reduced odds of olfactory impairment.[6] (**Table IX-31**) Omega-3 supplementation is a therapeutic option in the setting of postoperative olfactory loss, with the potential to improve

the course of olfactory dysfunction from other inflammatory etiologies. Additional study is needed to evaluate appropriate treatment protocols and the impact of omega-3 LCPUFAs on other forms of olfactory dysfunction.

Table IX-31 Use of Omega-3 to Treat Olfactory Dysfunction

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Yan et al[5]	2020	1b	Randomized controlled trial	87 patients with sellar/parasellar tumors randomized to 1) Nasal saline irrigation (n=41) 2) Nasal saline irrigation and omega-3 supplementation (n=46)	Post-operative UPSIT at: 1) 6 weeks 2) 3 months 3) 6 months	Omega-3 protective against olfactory loss 6-months following sellar/parasellar surgery (OR 0.005, 95%CI 0.003-0.81, P=.03)
Mazahery et al[7]	2019	3*	Randomized controlled trial	117 children with autism spectrum disorder randomized to 1) Vitamin D (n=31) 2) Omega-3 (n=29) 3) Both (n=28) 4) Placebo (n=29)	SPM-taste and smell at baseline and 12 month follow-up	Omega-3 LCPUFA with vitamin D is not shown to impact subjective smell and taste in children with autism spectrum disorder, (score change −2.3, 95%CI −4.7-0.1, P=0.06)
Gopinath et al[6]	2015	3	Population-based observational cohort study	667 suburban Australians with cross-sectional dietary and olfaction data collected from FFQ and SDOIT olfactory test	SDOIT baseline and 5-year follow-up	Adults >60 years of age with the highest consumption of nuts and fish had reduced odds of olfactory impairment, independent of potential confounding. (adjusted OR 0.66, 95% CI 0.44, 0.97)

*LOE downgraded due to differences in population (pediatric autism) and differences in outcome measures (SPM-taste and smell). FFQ = Food-Frequency Questionnaire; LCPUFA = long chain polyunsaturated fatty acids; SDOIT = San Diego Odor Identification Test; SPM = Sensory Processing Measure; UPSIT = University of Pennsylvania Smell Identification Test.

Use of Omega-3 for Treatment of Olfactory Dysfunction

Aggregate Grade of Evidence: B (Level 1b: 1 study; Level 3: 2 studies)

Benefit: Protection against olfactory loss after endoscopic skull base surgery as well as potentially protective for other etiologies of smell loss, for example, in an aging

population.
Harm: Mild side effects, if any including unpleasant taste, headache, gastrointestinal symptoms. Should not be used in patients with underlying bleeding disorders or on other blood thinning agents, as can also decrease clotting ability.
Cost: Generally low cost pharmacotherapy.
Benefits-Harm assessment: There is a benefit over placebo in protection from olfactory loss in patients who undergo endoscopic resection of sellar and parasellar masses as long as patients do not have underlying bleeding disorders, are on other blood thinning agents or cannot tolerate other minor side effects.
Value Judgments: It remains uncertain whether omega-3 supplementation may be beneficial in other etiologies of olfactory loss other than endoscopic resection of sellar and parasellar masses.
Policy level: Recommendation for use of omega-3 in treating OD seen after endoscopic skull base surgery. It remains an **option** for treating other etiologies of OD.
Intervention: Omega-3 supplementation can be used to treat OD in patients after endoscopic skull base surgery and is an option for possible protection against other etiologies of olfactory loss. Additional RCTs with expanded etiologies of olfactory loss are warranted to prospectively evaluate clinical efficacy and treatment regimens.

SECTION: IX. Management
F. If no underlying disease state to correct:
4. Vitamins and supplements
b. Zinc

Zinc is involved in cell proliferation and is potentially an important element in maintaining olfactory function.[1] Zinc sulphate was studied by Aiba et al[2] and Quint et al[3] for patients with post viral olfactory dysfunction. Aiba et al showed that there was no subjective difference between their treatment arms. No objective measure was used, follow up interval was not reported, and adverse reactions were not discussed. Similarly, Quint et al did not find a significant improvement. The response rates are in keeping with placebo or spontaneous recovery, highlighting the lack of evidence supporting the use of zinc sulphate.[1–6] Lyckholm et al[1] found zinc ineffective, and potentially with an adverse impact, when treating post chemotherapy anosmia in a small placebo-controlled RCT. Jiang et al[6] found in post-traumatic olfactory loss increased recovery rates in patients treated with zinc gluconate when compared to controls.[7]

At oral doses traditionally used for chemosensory dysfunction, zinc can have side effects such as iron deficiency anemia, copper deficiency, gastric distress, neutropenia and impaired immune function.[7]

Intranasal zinc administration is marketed as a treatment for the common cold, and there are multiple low quality, small studies highlighting zinc-induced permanent anosmia. Eby et al[8] proposed that it would be unethical to introduce zinc to the interior of the nose.

Table IX-32. Use of Zinc to Treat Olfactory Dysfunction

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Harless et al[4]	2016	1	Systematic Review	Pharmacological treatments for the management of post-viral olfactory dysfunction	Most common assessment – Sniffin' Sticks	8 articles were included, yielding 563 patients. Zinc sulphate did not show significant improvement in both subjective symptom scores and objective scores, including with Sniffin' Sticks.
Jiang et al[6]	2015	2	Prospective randomized study	Patient cohort – post traumatic anosmia (N = 145) 1) Zinc gluconate and prednisolone (N = 39) 2) Zinc gluconate (N = 35) 3) Prednisolone (N = 34) 4) No medication (N = 37)	6 month trial Phenyl ethyl alcohol threshold testing	The recovery rates of olfactory function of groups 1 and 2 were significantly higher than the recovery rate of group 4 (Group 3 also showed recovery, and was not significantly different when compared to group 1 and 2). Improvement could be due to the use of prednisolone rather than zinc.
Lyckholm et al[1]	2012	2	Double-blinded, placebo-controlled, randomized clinical trial	Post chemotherapy patient cohort (N = 58)	3 month follow up Patient questionnaire	No statistically significant difference in the two study groups in loss or distortion of smell. A trend towards

				1) Zinc sulphate 220mg orally twice daily (N =20) 2) Placebo (N = 21)	using 1-100 scale.	nonsignificant *worsening* in loss of smell over time in zinc study group.
Quint et al[3]	2002	3	Prospective clinical trial	Patient cohort – non-conductive olfactory disorders (N = 77) 1) Caroverine 120mg/day (N = 51) 2) Zinc sulphate 400mg/day (N = 56)	4-week study Assessment of n-butanol odor threshold and odor identification	The use of zinc sulphate did not produce any significant measurable improvement in olfaction.
Aiba et al[2]	1998	3	Retrospective, nonblinded, noncontrolled, parallel group clinical trial	Patient cohort – sensorineural olfactory loss (post-viral, post traumatic or unknown) (N = 426) 1) Zinc sulphate 300mg daily (N = 25) 2) Zinc sulphate plus topical corticosteroids and oral vitamin B (N = 142) 3) Topical corticosteroids and vitamin B (N = 259)	Follow up time unclear but listed as at least one month Subjective symptom improvement based on 7 point scale.	50% of patients with PVOD reported subjective mild to significant improvement, but no statistical difference between the groups. No association with pretreatment serum zinc levels. Adverse effects not discussed.
Henkin et al[5]	1976	3	Double-blinded, crossover trial	Patient cohort – Variety of etiological factors	6 months Forced-choice, three stimulus	No statistically significant effects of zinc on either taste or smell function were found

				for olfactory loss (N = 106) Crossover between placebo and zinc gluconate	sniff test	

Use of Zinc to Treat Olfactory Dysfunction

Aggregate Grade of Evidence: B (Level 1: 1 study; Level 2: 2 studies; Level 3: 3 studies)

Benefit: In patients with olfactory dysfunction, the response rate of symptoms to oral zinc supplements is similar to spontaneous recovery, with no statistically significant improvement, except in one study assessing post traumatic dysfunction. Intranasal zinc treatment shows no benefit and likely harm.

Harm: Iron deficiency anemia, copper deficiency, gastric distress, neutropenia and impaired immune function in select patients. Possible irreversible anosmia with intranasal application.

Cost: Minimal

Benefits-Harm assessment: There is no advantage of using either oral or intranasal zinc treatment in patients with olfactory dysfunction (OD), with no consolidated evidence of statistically significant improvements, and potential minor harm caused by oral zinc and significant potential harm caused by intranasal zinc.

Value Judgments: There does not appear to be any value added by using zinc in the treatment of most forms of OD.

Policy level: Oral zinc treatment for post-traumatic OD: **option.** Oral zinc treatment for non-post-traumatic OD: **recommendation against.** Intranasal zinc treatment: **recommendation against.**

Intervention: Zinc treatment should not currently be used to treat most patients with OD.

SECTION: IX. Management

F. If no underlying disease state to correct:

4. Vitamins and supplements

c. Alpha lipoic acid

Typically used as a nutritional supplement and antioxidant for diabetic neuropathy, alpha-lipoic acid was considered a candidate for olfactory recovery with increased expression of nerve growth factor, substance P and neuropeptide Y. It also has neuroprotective capabilities which may prevent neural damage involving free radicals.

Only one study has examined the use of alpha lipoic acid in olfactory loss. Hummel et al[1] conducted a prospective, unblinded, non-controlled trial using alpha lipoic acid treatment (600 mg daily) in 23 patients with post-viral olfactory dysfunction. After a median of 4 months of treatment, 61% of patients demonstrated some improvement in TDI scores, with 35%

improving by more than 5.5. A weak correlation was seen between age less than 60 and improved recovery. With no control group, and no time from loss restriction, spontaneous improvement cannot be ruled out. No patients in the study reported severe adverse reactions. The use of alpha lipoic acid is normally well tolerated, with a small risk of nausea, rash and liver enzyme elevation at high doses. Patients with diabetes have a small risk of medication interaction and hypoglycemia. No other study has been completed to support this finding.

Table IX-33. Use of Alpha-Lipoic Acid to Treat Olfactory Dysfunction

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Hummel et al[1]	2002	4	Prospective observational study (N=23)	3) Anosmia Alpha Lipoic Acid 600mg daily 4) Hyposmia Alpha Lipoic Acid 600mg daily	Median follow up 4 months (3-11) Sniffin' Sticks (TDI Score)	35% had an increase in TDI score by at least 5.5. Threshold only sub-score to reach significance. Negative correlation with age and improvement.

Use of Alpha-Lipoic Acid to Treat Olfactory Dysfunction
Aggregate Grade of Evidence: D (Level 4: 1 study)
Benefit: Potential improvement in olfactory function (primarily threshold).
Harm: Low risk of hypoglycemia, nausea.
Cost: Minimal - $1/day for 600mg dose
Benefits-Harm assessment: Not enough data to interpret potential benefit, relatively low harm.
Value Judgments: Not enough evidence exists to support value in use for OD.
Policy level: No recommendation for use of alpha-lipoic acid to treat olfactory dysfunction.

Intervention: More data is needed before clinicians can present this as a beneficial treatment option for their patients.

SECTION: IX. Management
F. If no underlying disease state to correct:
4. Vitamins and supplements
d. Vitamin A

In humans, only five studies have focused on the role of vitamin A in olfaction. The first of these studies, a case series reported by Duncan and Briggs, reported beneficial effect with high-dose systemic vitamin A therapy in 50 out of 56 patients.[1] Another study showed that oral substitution of vitamin A at 10,000 micrograms per day for 4 weeks cured olfactory loss in patients with liver cirrhosis and vitamin A deficiency.[2] More recently, however, a double-blind placebo controlled trial by Reden and colleagues[3] using a more moderate oral dose of 10,000 I.U./d for 3 months, reported no significant improvement in olfactory test scores following treatment with oral vitamin A.[3] Kartal et al[4] observed a significant improvement in odor identification after a non-controlled 3-month systemic treatment with isotretinoin (synthetic analogue of vitamin A) in acne patients. More convincing evidence comes from a retrospective controlled study with local vitamin A application.[5] The combined therapy of olfactory training with intranasal vitamin A in a dose of 10,000 IU per day for 2 months produced significantly greater improvement compared to pure olfactory training in patients with post-infectious smell loss. Further, a randomized, controlled study with a similar experimental approach (vitamin A at 10,000 I.U. per day with olfactory training vs. vitamin A vs. standard therapy) is currently being carried out in Canada with a large number of patients and different aetiologies of olfactory loss (post-infectious, post-traumatic, and sinonasal) (ClinicalTrials.gov Identifier: NCT03574701).[6]

Table IX.34. Use of Vitamin A to Treat Olfactory Dysfunction

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion

Duncan and Briggs[1]	1962	4	Case series over a period of 15 years with differences in interventions	Patients with olfactory disorders (eg., post-infectious, post-traumatic, idiopathic; n=56) treated with high-dose systemic vitamin A therapy (injection, tablets, oral emulsion; 50,000-150,000 IU/d) for up to 12 weeks	Subjective olfactory improvement	Improvement in odor detection in 50 out of 56 patients
Garrett-Laster et al[2]	1984	4	Descriptive (non-controlled) study	Vitamin A deficient patients (n=27) treated with oral vitamin A (10,000 micrograms/d) for 4 weeks	Pyridine detection and recognition threshold improvement	Significant improvement in olfactory threshold
Reden et al3	2012	2	Double-blind, placebo-controlled, randomized clinical trial	Patients with post-infectious or post-traumatic olfactory disorder (n=52) receiving either oral 1) Vitamin A at a dose of 10,000 I.U./d or 2) placebo for 3 months	Improvement in comprehensive odor threshold, discrimination, and identification (TDI) score (Sniffin`Sticks comprehensive test)	No significant difference between placebo and verum groups regarding the TDI-change and subfunction (threshold/discrimination/identification)-change after treatment
Kartal et al[4]	2017	4	Descriptive (non-controlled) study	Patients with acne (n=33) treated with oral isotretinoin (0.5-0.8 mg/kg per	Improvement in odor identification (Sniffin`Sticks screening test)	Significant improvement in odor identification

				day) for 3 months		
Hummel et al[5]	2017	4	Retrospective cohort analysis	Patients with post-infectious (n=102) or post-traumatic (n=68) olfactory disorder (n=170) 1) treated with topical vitamin A 10,000 IU once daily, for 8 weeks and performing olfactory training for 12 weeks 2) performing olfactory training for 12 weeks only	Improvement in comprehensive odor threshold, discrimination, and identification (TDI) score (Sniffin`Sticks comprehensive test)	Olfactory training + vitamin A produced significantly greater improvement compared with training alone, in discrimination score for all patients and in threshold and discrimination in the post-infectious group; In the post-infectious group, significantly more patients improved their general olfactory function with combined therapy compared to training alone

Use of Vitamin A treatment for olfactory dysfunction.

Aggregate Grade of Evidence: C (Level 2: 1 study, Level 4: 4 studies)

Benefit: Local topical vitamin A application led to an improvement in olfactory function in patients with post-infectious smell loss, but these are low-evidence studies. The effect was less pronounced in post-traumatic patients, but also present. No benefit seen for systemic Vitamin A.

Harm: Potential local irritation. Potential for vitamin toxicity if taken systemically. (Contraindication for people with peanut allergy when using peanut oil as an additive)

Cost: Very low therapy costs.

Benefits-Harm assessment: Potential benefit of local vitamin A treatment for olfactory dysfunction likely outweighs potential for local irritation in nasal cavity. No benefit for systemic Vitamin A.

Value Judgments: In contrast to the potential added value of local vitamin A treatment in OD, the evidence does not support even potential benefit for systemic treatment (3 case series and non-controlled studies and evidence of a lack of effectiveness in 1 RCT), so this modality holds no value.

Policy level-Use of local application of Vitamin A is an **option** in patients with post-infectious and post-traumatic olfactory dysfunction. Use of systemic Vitamin A is **recommended against.**

Intervention-The potential benefit of topical Vitamin A and the potential for local irritation can be discussed with the patient and if the shared decision making process leads to choosing this

option for treatment, it can be administered intranasally with the patient in the Kaiteki position at a dose of 10,000 IU once daily, for 8 weeks.

SECTION: IX. Management
F. If no underlying disease state to correct:
4. Vitamins and supplements
e. Tokishakuyakusan

Tokishakuyakusan (TSS), a traditional Japanese herbal drug (combination of six medical plants: Japanese Angelicae Root, Peony Root, Cnidium Rhizoma, Atractylodes Lanceae Rhizoma, Alismatis Rhizome and Pria Sclerotium), has been widely used in Japan for the treatment of patients with gynecological disorders, including climacteric disturbance, menstrual irregularity, dysmenorrhea, and infertility. It has also been approved for the above diseases by the Japanese Ministry of Health, Labor and Welfare. In recent years, TSS has also been prescribed in Japan for patients with post-infectious olfactory dysfunction (PIOD) and has shown efficacy in improving olfactory function, although the studies are all low level of evidence. Recent clinical practice guidelines [1] published by the Japanese Rhinologic Society stated that TSS may be effective for the treatment of PIOD, but placebo-controlled studies are necessary to accurately evaluate the effect of these drugs on PIOD. Miwa et al[2] reported that the treatment of PIOD with TSS resulted in a greater improvement in olfactory function than that seen with intranasal steroid treatment. Uchida et al[3] treated patients with PIOD, who had not responded to intranasal steroids, with TSS or Ninjin'yoeito, another Japanese herbal medicine, and the improvement rate was 43% and 36%, respectively. Ogawa et al[4] also reported that the improvement rate of patients with post-URTI dysfunction, who received treatment with intranasal steroid treatment alone, TSS oral administration alone, or a combination of steroids and TSS, for 3 months, was 29%, 55%, and 60%, respectively. Most recently, Ogawa et al[5] reported additionally on the time-course of olfactory recovery and the prognostic factors in PIOD patients treated with TSS. They revealed the recovery of olfactory function often occurred during the early period, less than 6 months from symptom onset, but the number of patients with recovery of olfactory function increased for long-term symptoms 24 months after the first visit. This study also reported that residual olfactory function and younger age were prognostic factors for recovery

of olfactory function.[5] Unfortunately, all of these studies are case series, with no placebo control group and no timing restriction for enrollment, and therefore the potential for spontaneous resolution or other biases to confound these findings make this data currently inconclusive.

Table IX-35. Use of Tokishakuyakusan for Treatment of Olfactory Dysfunction

Study	Year	Level of Evidence	Drug	Study Design	Study Groups	Clinical Endpoint	Conclusions
Miwa et al[2]	2005	4	TSS	Case-series	(n=60) Patients with PIOD & post-traumatic olfactory dysfunctions	Olfactory function (T&T olfactometer)	TSS resulted in a greater improvement in olfactory function than that seen with intranasal steroid treatment.
Uchida et al[3]	2009	4	TSS	Case-series	(n=31) Patients with olfactory dysfunctions	Olfactory function (T&T olfactometer)	43% of PIOD patients who had not responded to intranasal steroids improved with TSS.
Ogawa et al[4]	2010	4	TSS	Case-series	(n=30) Patients with PIOD	Olfactory function (T&T olfactometer)	The improvement rate of patients who received treatment with intranasal steroid treatment alone, TSS oral administration alone, or a combination of steroids and TSS, for 3 months, was 29%, 55%, and 60%, respectively.

Ogawa et al[5]	2020	4	TSS	Case-series	(n=82) Patients with PIOD	Olfactory function (T&T olfactometer)	The cumulative olfactory recovery rate at 6, 12 and 24 were 47.3%, 62.7% and 77.3%. The cumulative olfactory cured rate in same periods were 23.6%, 33.7% and 61.0%. Residual olfactory function and younger age were prognostic factors.

Use of TSS for Treatment of Olfactory Dysfunction
Aggregate Grade of Evidence: C (Level 4: 4 studies)
Benefit: Objective olfactory test revealed the improvement of olfactory function by oral TSS administration. Lack of consideration for spontaneous improvements, lack of control populations, and validated assessment tools limit the interpretability of results.
Harm: There was no adverse event reported in these specific studies. An unknown frequency of the following symptoms has been reported in relation with general use of TSS: loss of appetite, stomach discomfort, nausea, vomiting, abdominal pain, diarrhea, rash, skin itching and *liver function abnormality.*
Costs: Low.
Benefits-Harm Assessment: Inconclusive benefits with limited, but potential, harm.
Value Judgments: Although preliminary studies suggest the benefit of TSS for POID, a higher level of evidence with controlled studies is needed to accurately evaluate the effect of this medication.
Policy Level: No recommendation can be made at this time regarding use of TSS for olfactory dysfunction.
Intervention: Well-designed studies using timing restriction for enrollment, controls and validated measures to obtain higher level of evidence is needed.

SECTION: IX. Management
F. If no underlying disease state to correct:

5. Minocycline

Minocycline is a second generation tetracycline antibiotic that has been in use for over thirty years, primarily for the management of acne vulgaris and sexually transmitted diseases.[1] Minocycline, and the related drug doxycycline, exhibit mechanisms of action beyond their anti-bacterial effects including anti-inflammatory, anti-apoptotic and immunomodulatory effects suggesting a potential role in the clinical management of dermatitis, periodontitis, rheumatoid arthritis, inflammatory bowel disease, allergic asthma, atherosclerosis and chronic rhinosinusitis.[2,3] Both drugs are well-tolerated with a low side effect profile enabling their long-term use in chronic disorders.[4] Minocycline is also particularly lipophilic with excellent penetration of the central nervous system, hence the potential for treatment of neurologic disorders ranging from trauma to neurodegenerative diseases.[5] These properties suggested that minocycline could play a role in the management of olfactory disorders as well.

Minocycline was first evaluated as a neuroprotective agent in an animal model of anosmia almost 20 years ago.[6] This study removed the olfactory bulb of rats, which reliably produced rapid apoptosis of the peripheral olfactory sensory neurons (OSNs). Although the results indicated that minocycline did not prevent apoptosis, the time course was significantly delayed suggesting the possibility that lesser degrees of injury might respond to minocycline. Moreover, the limited data available suggest that apoptosis is a common pathway for a range of human olfactory disorders, leading those authors to suggest that minocycline might serve as a broadly effective treatment for smell loss.[7–9]

Based on this theoretical rationale, as well as an excellent safety profile, a human trial of minocycline for the management of post viral olfactory loss was undertaken. A total of 55 patients were randomized in a prospective double-blind controlled trial of 50mg minocycline twice daily for 3 weeks and were followed for 7 months. The duration of olfactory loss was not reported. Unfortunately, there was no difference between groups in TDI score but both groups demonstrated baseline improvement in olfactory performance over those 7 months.[10] The reasons for failure are uncertain and may be related to the pathophysiology or duration of olfactory loss in post-infectious olfactory disorders. The anti-inflammatory and neuroprotective properties of minocycline are currently being studied in a number of trials for an array of

neurologic disorders, some of which have associated olfactory deficits. If minocycline, or another neuroprotective agent, is shown to be effective in reversing olfactory loss associated with the primary neurologic disorder, it is possible that the use of this agent specifically for olfactory disease could be revisited, but currently there is no evidence that it should be recommended for these patients.

Table IX.36. Use of Minocycline to Treat Olfactory Dysfunction

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Reden et al[10]	2011	1b	Randomized, prospective, double-blind, placebo-controlled trial	Patients with post-infectious olfactory dysfunction (n=55) receiving either 1) minocycline (2 × 50 mg/d) 2) placebo for 3 weeks	Improvement in odor identification (Sniffin' Sticks screening test)	Minocycline in the given dosage has little or no effect on the recovery of human olfactory function following postinfectious olfactory loss. However, spontaneous recovery is found in approximately 20% of the patients over an observation period of 7 months

Use of Micocycline for treatment of Olfactory Dysfunction
Aggregate Grade of Evidence: B (Level 1b: 1 study)
Benefit: None
Harm: Minimal as minocycline has a very low side effect profile
Cost: Low
Benefits-Harm assessment: Slight harm possible related to low side effect profile
Value Judgments: Despite theoretical efficacy, no improvement was observed at the dose and duration used in the trial.
Policy level: Recommendation against the use of minocycline for post-infectious olfactory dysfunction.
Intervention-Minocycline should not currently be offered to patients with olfactory dysfunction.

SECTION: XI. Management
F. If no underlying disease state to correct:
6. Theophylline

Odorants bind to G-protein coupled receptors within the olfactory epithelium and trigger an increase in intracellular cyclic adenosine monophosphate (cAMP). This increase leads to depolarization and a signal transduction cascade to the olfactory bulb. Phosphodiesterase inhibitors (PDEIs) increase intracellular cAMP and cGMP by preventing their degradation. As such, there is a compelling mechanism by which PDEIs could potentially enhance olfactory signal transduction in patients with olfactory dysfunction.

The clinical evidence for PDEIs, however, is mixed. In 2009, an open-label case series of 312 hyposmic patients by Henkin et al. showed that 50.3% of patients had a five percent or greater subjective improvement in olfaction after oral theophylline treatment (200-800 mg/day) and 21.7% of these reported that their olfactory function returned to normal.[1] This study was not carried out with validated olfaction measures, controls or strict selection criteria so no definite conclusion can be made from it. Challenges with oral theophylline, including tolerance and toxicity, with high levels of drug-drug interactions, lead to a follow up open label case series using topical, intranasal theophylline. This study also showed improvement in olfactory function in 8 of 10 subjects after 4 weeks of treatment, but suffered from the same weaknesses as the prior.[2] Most recently, in an open-label clinical trial of a very small number of patients with end stage renal disease and olfactory dysfunction, 5 of 7 patients improved with topical, intranasal theophylline (20 micrograms/d for 6 weeks), although this minimal improvement was below the MCID.[3]

Theophylline is the most investigated PDEI in the treatment of olfactory dysfunction, however caffeine, sildenafil, and pentoxifylline have also been studied. In a double-blind, placebo-controlled trial of 76 patients with hyposmia, a single dose of 65mg of caffeine (e.g., espresso) showed no effect on olfactory function.[4] Additionally, a trial of 20 healthy male volunteers also found no effect of sildenafil on olfaction at 50mg and, surprisingly, decreased olfactory function was seen at 100mg presumably due to nasal congestion.[5] Furthermore, pentoxifylline administered (IV or oral) in 19 patients with otologic conditions demonstrated some improvement in odor threshold scores, however overall objective olfactory measures did not improve.[6] Most recently, 6 patients with post-traumatic hyposmia were administered

200mg/day of this medication, with some small non-significant improvements in odor threshold and identification scores.[7]

Although there is some level 2-4 evidence to suggest that theophylline may provide sub-minimally clinical important difference improvement in olfactory function by both oral and topical administrations, definitive conclusions are not able to be made due to limitations in study design. Specifically, these studies do not account for spontaneous olfactory recovery given the lack of control arm, include a heterogenous group of olfactory loss etiologies and rely on subjective assessments rather than validated instruments. PDEIs other than theophylline (e.g., caffeine, sildenafil, and pentoxifylline) have not been shown to provide clinically meaningful benefit in patients in the treatment of olfactory loss.

Table IX-37. Use of Theophylline or other PDEIs to Treat Olfactory Dysfunction

Study	Year	Level of Evidence	Drug	Study Design	Study Groups	Clinical Endpoint	Conclusions
Levy et al[8]	1998	4	Oral Theophylline 250-500mg daily	Case-series	(n=4) Patients with hyposmia (male)	Functional brain activation in response to odorant stimulation	Oral theophylline for 4-6 months may improve functional brain activation in response to odorant stimulation.
Gudziol et al[5]	2007	2	Sildenafil 50mg and 100mg daily	Double-blinded, placebo-controlled, crossover study	(n=20) healthy controls (male)	Olfactory function (Sniffin Sticks)	There is a dose-dependent response to 8 days of sildenafil. 50mg had no effect, whereas 100mg dose showed decreased objective olfactory function presumably due to

							constricted airflow.
Gudziol et al[6]	2009	4	Pentoxifylline Intravenous 400 and 600mg daily	Case-series	(n=19) Patients with inner ear conditions (6 with hyposmia)	Olfactory function (Sniffin Sticks)	Significant objective improvement in odor thresholds were seen in patients with hyposmia being treated for unknown duration for inner ear disease.
Henkin et al[1]	2009	4	Oral Theophylline 200-800mg daily	Case-series	(n=312) Patients with hyposmia	Subjective and objective psychophysical measurements	50.3% of patients were responsive to treatment for 2-10 months based on >5% subjective improvement.
Henkin et al[9]	2011	4	Oral Theophylline 200-800mg daily	Case-series	(n=31) Patients with hyposmia with available pre- and post-treatment cAMP and cGMP and theophylline levels	Subjective and objective psychophysical measurements	Low levels of cAMP and cGMP within nasal mucus may predict lack of response to oral theophylline with 2-10 months of treatment.
Henkin et al[2]	2012	4	Intranasal Theophylline 20 mcg each naris daily	Case-series	(n=10); Patients with hyposmia and hypogeusia	Subjective and objective psychophysical measurements	Intranasal theophylline for up to 4 weeks may improve objective odor detection and recognition thresholds.

Meusel et al[4]	2016	2	Caffeine 65mg once	Double-blind, placebo-controlled trial	(n=76); Patients with hyposmia	Olfactory function (Sniffin Sticks)	Single administration of caffeine had no effect on objective olfactory function.
Henkin et al[10]	2017	4	Oral Theophylline 200-800mg daily	Case-series	(n=58); Patients with hyposmia (n=44) and healthy controls (n=14)	Subjective and objective psychophysical measurements	Objective Shh levels in nasal mucus were associated with subjective improvement in olfaction after 2-10 months of treatment.
Nigwekar et al[3]	2017	4	Intranasal Theophylline 20 mcg each naris daily	Case-series	(n=7) Patients with ESRD and mild olfactory dysfunction	Odor Identification (UPSIT)	Intranasal theophylline for 6 weeks yielded minimal objective improvement of odor identification in 5 of 7 patients with ESRD and hyposmia - *though below MCID.*
Stafford et al[11]	2020	3	Caffeine	Cohort study	Coffee consumers (n=41) and non-consumers (N=21) with normal olfaction	Threshold tests for coffee odors	Regular consumers of coffee had an enhanced sensitivity to coffee odor by objective testing.
Whitcroft et al[7]	2020	4	Pentoxifylline Oral, 600mg daily	Case-series	(n=6) Patients post-traumatic hyposmia	Olfactory function (Sniffin Sticks)	Oral pentoxifylline for 21 days did not appear to be beneficial in the treatment of hyposmia in this group.

Use of Theophylline or other PDEIs to Treat Olfactory Dysfunction
Aggregate Grade of Evidence for systemic PDEIs: C (Level 2: 2 studies; Level 3: 1 study; Level 4: 6 studies)
Aggregate Grade of Evidence for intranasal theophylline: D (Level 4: 2 studies)
Benefit: Inconclusive evidence that olfactory function improves with oral or topical administration of PDEIs. Lack of consideration for spontaneous improvements, lack of control populations, and validated assessment tools limit the interpretability of results.
Harm: Described adverse events include restlessness, tachycardia, nausea, anorexia, gastrointestinal discomfort, sleep disturbance. These may be less significant with topical administration.
Costs: Low, as the oral PDEIs are available in generic form and FDA approved in other conditions (e.g., asthma, bronchitis, emphysema, erectile dysfunction, and insomnia). Intranasal theophylline is not commercially available as an FDA approved medication.
Benefits-Harm Assessment: The potential for harm from oral PDEIs outweighs the potential benefit. There is not enough evidence to assess benefit versus harm for topical theophylline.
Value Judgments: The evidence for the use of oral PDEIs in olfactory dysfunction is inconclusive and that there exists potential for harm. The evidence for topical theophylline is inconclusive and warrants further investigation.
Policy Level: Recommendation against oral PDEIs for use in treating olfactory dysfunction. **No recommendation** can be currently made regarding use of intranasal theophylline to treat olfactory dysfunction.
Intervention: Oral PDEIs should not be recommended in patients with olfactory dysfunction as the potential for benefit is inconclusive and there exists potential for harm. Providers should inform their patients that the evidence for intranasal theophylline is preliminary and inconclusive before considering its use.

SECTION: XI. Management
F. If no underlying disease state to correct:
7. Intranasal insulin

Insulin receptors are found throughout the human body, including the central nervous system. In the brain, insulin receptors have been noted to be present within the olfactory bulb, and the administration of intranasal insulin has been shown to traverse the cribriform plate via olfactory nerves.[1] However, the effect of insulin on olfaction is not clearly established. Ketterer et al[2] revealed that creating a hyperinsulinemic state with sustained euglycemia leads to a worsened olfactory threshold (reduced sensitivity) on Sniffin' Sticks testing (threshold reduced by -1.6) in healthy subjects versus fasting controls.[2] Brunner et al[3] also demonstrated in a controlled study that a single dose of 40 IU of intranasal insulin in normosmic subjects worsened threshold (threshold reduced by -1.3 versus saline) on n-Butanol testing, but had no

effect on discrimination. Conversely, Thanarajah et al[4] found an improved threshold with intranasal insulin that was related to both insulin sensitivity and the intranasal dose applied. Intranasal insulin has also been shown to increase satiety and reduce caloric intake in healthy women, presumably by reducing peripheral olfactory function.[5]

Two studies evaluating intranasal insulin for olfactory dysfunction were included in analysis (**Table IX-38**). Rezaeian et al[6] evaluated the therapeutic effects of intranasal insulin on patients with undifferentiated hyposmia using a double-blinded, randomized controlled trial. Absorbable dressing impregnated with 40 IU insulin or saline was placed endoscopically twice weekly for 4 weeks into the olfactory cleft. 36 patients with undifferentiated olfactory loss for > 6 months completed the trial. A significant improvement was seen on butanol threshold testing in the treatment group (+1.11) without a significant effect on serum insulin or glucose. Schöpf et al[7] found a similar outcome with a single dose of 40 IU of intranasal insulin in a pilot study of 10 patients with post-infectious olfactory dysfunction for greater than 1 year. 60% of the patients had a minimally increased performance in olfactory threshold on Sniffin' Sticks testing (+1) 30 minutes after application, but TDI and all sub-domain scores were not significantly changed. They did, however, find a correlation between score improvement (TDI and identification) after intranasal insulin in patients with increased BMI.

The mechanism of action for improvement in olfactory dysfunction versus impairment in healthy controls has not been established. One proposed theory is increased cyclic AMP and GMP within the olfactory neuroepithelium secondary to intranasal insulin application.[8]

Table IX-38. Use of Intranasal Insulin to Treat Olfactory Dysfunction.

Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Rezaeian et al[6]	2018	2	RCT	38 patients with undifferentiated hyposmia for >6 months. 36 completed evaluation. 1) gelfoam with 40IU insulin (n=18) 2) saline soaked gelfoam (n=18) placed in olfactory cleft twice weekly for 4w	1)Butanol threshold test (0-7) 2) Serum insulin and glucose levels	Very slightly improved olfactory threshold. (+1.11vs -0.02) No change in serum insulin or glucose levels in either group
Schöpf et al[7]	2015	3	Prospective pilot study	Ten patients with PIOD. 1)Single dose of 40IU intranasal insulin. (n=10) 2) saline 1y later (n=7)	1)Sniffin' Sticks 2)Olfactory intensity 3)Hedonic rating	1) No significant change in TDI score or each individual domain. Threshold score minimally improved in 6 patients (+1). 2) Increased intensity score after insulin. 3) No change in hedonic rating. Strong correlation with BMI and improved olfactory scores with insulin.

Use of Intranasal Insulin to Treat Olfactory Dsyfunction
Aggregate Level of Evidence: C (1 Level 2, 1 Level 3).
Benefit: Modest improvement in threshold
Harm: None currently known

Cost: Procedural cost for placement of intranasal gelfoam. Small cost for intranasal insulin spray and gelfoam.
Benefits-Harm Assessment: Possible benefit in modest olfactory recovery, although evidence is mixed.
Value Judgments: Unknown.
Policy Level: No recommendation
Intervention: Further investigation of intranasal insulin for olfactory dysfunction is warranted. Limited evidence currently exists.

SECTION: XI. Management
F. If no underlying disease state to correct:
8. Platelet rich plasma

The use of platelet-rich plasma (PRP) as a treatment option for olfactory dysfunction has not been well established, but pilot studies have demonstrated safety and potential efficacy.[1–3] PRP is an autologous blood product containing supraphysiologic concentrations of platelets with neurotrophic and anti-inflammatory properties that have shown promise in neural regeneration in other peripheral neuropathies.[4–9] A murine model of anosmia treated with topical PRP demonstrated improved olfactory function and decreased olfactory epithelial damage.[10] Two small human studies used PRP for treatment of olfactory dysfunction with no adverse outcomes including no worsening smell function.[1,2] Most recently, a small case-series of subjects with recalcitrant olfactory loss (>6 but <12 months) showed statistically significant olfactory improvement at 3 months post-treatment, although the number of patients was extremely limited and there was no control group, so no definite conclusion could be reached.[1] Although not uniquely targeting subjects with olfactory dysfunction, treatment of platelet-rich fibrin (second generation PRP) during septoplasty demonstrated improved olfactory outcomes in the early post-operative period compared to no treatment with no differences seen at 6 weeks, possibly reflecting the anti-inflammatory properties of PRP.[3]
PRP has very preliminary potential to improve treatment-resistant olfactory dysfunction, particularly for those with hyposmia. Further research in PRP's biological effects on olfactory nerve regeneration as well as large, randomized controlled clinical trials evaluating clinical safety and efficacy are warranted, and a multi-center randomized controlled trial examining

multiple injections of PRP versus saline to treat post-viral olfactory dysfunction is currently underway in the United States (NCT04406584).[11]

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Table IX-39. Evidence for Platelet-Rich Plasma Injection for the Treatment of Olfactory Dysfunction

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Yan et al[1]	2020	4	Prospective single-arm pilot case-series study	• 7 pts with olfactory loss >6mo but < 12mo, no evidence of sinonasal inflammatory disease, had failed to improve with olfactory training and topical steroid rinses. • Single 1mL PRP injection in bilateral olfactory clefts.	• Sniffin' Sticks TDI* at 1 and 3 months	• No adverse events. • TDI scores improved from mean baseline 19.5 to 23.6 at 3 mo • Hyposmic subjects (16 < TDI < 30) improved by 5.85 at 3 months, most significantly in the threshold sub-component • 2 pts with anosmia (TDI < 16) with no significant improvement. • Did not control for spontaneous recovery
Mavrogeni et al[2]	2016	4	Prospective single-arm case-series study	• 5 pts w "severe anosmia" without known duration, unresponsive to prior treatment, with no CT abnormalities (1 post-traumatic, 4 post-viral smell loss) • 3 olfactory groove injections 4 weeks apart, with a 4th injection 3 months later	• Self-reported symptom score and authors' version of a smell identification + discrimination test • 10 point total score	• 4 of 5 pts reported "their smell came back." • Mean pre-treatment score: 0.19, mean post-treatment score: 4.92 • Did not control for spontaneous recovery
Tutar et al[3]	2020	2B	Prospective randomized clinical study	• Pts undergoing septoplasty for nasal obstruction and septal deviation • 74 pts injected with platelet rich fibrin (PRF) at time of septoplasty vs. 67 pts no treatment	• Sniffin' Sticks TDI* at 1wk, 2wk, 6mo post-op	• Statistically significant difference in the number of hyposmic and normosmic patients in the groups with and without PRF treatment at 1 week. ($p < 0.05$)

				• Similar baseline distribution of anosmics (1.5 vs 1.4%), hyposmics (14.9 vs 12.2%), and normosmics (83.6 vs 86.5%) b/n the two groups		• No difference between groups at 6w or 6mo.
**Sniffin' Sticks (Burghardt®, Wedel, Germany) olfactory test, with threshold, discrimination, and identification measurements (TDI).						

Use of PRP Injections for Treatment of Olfactory Dysfunction
Aggregate Grade of Evidence: D (Level 2b: 1 study; Level 4: 2 studies)

Benefit: Platelet-rich plasma (PRP) injection represents a safe treatment for olfactory dysfunction with early but not well elucidated potential, particularly for hyposmic subjects with persistent loss
Harm: Discomfort and time commitment of the therapy as well as minimal risks of bleeding, infection, and theoretical risk of worsened smell loss, although this was not seen in pilot studies.
Cost: Moderate direct costs of PRP. Time off work for appointments and treatments
Benefits-Harm assessment: Early studies suggest potential for improvements in smell loss with minimal risk of harm, that warrant further investigation.
Value Judgments: Larger, randomized controlled trials are needed to demonstrate clinical benefits of PRP injection in smell loss.
Policy level: No Recommendation for the current use of PRP injection in treatment-refractory olfactory dysfunction**.**
Intervention: PRP injection in the olfactory cleft is worthy of further investigation for patients with olfactory dysfunction without sinonasal disease who have failed olfactory training and topical steroid therapy.

SECTION: XI. Management
G. Phantosmia/parosmia treatment
1. Medical treatment options

A systematic review of the literature for medical management of long-term phantosmia published in 2018 showed that very few studies have investigated medical management of phantosmia and even less on parosmia.[1] A small phone interview study of observation alone found that 57% of patients reported short-term improvement of symptoms while only 32% of patients reporting long-term relief.[2] Medical treatments have been evaluated in small cohort studies with variable success, including anti-psychotic medications,[3] anti-seizure medications,[4]

topical cocaine application,[5] or anti-migraine prophylactic medications.[6] **Table IX-40** shows a summary of the medical treatment modalities studied. A small study of migrainous patients retrospectively identified a link between some patients' headaches and phantosmia. Of the 14 patients in this cohort, nine demonstrated improvement in their phantosmia with anti-migraine prophylactic therapy, including topiramate, nortriptyline, and verapamil. In addition, none of the patients had headache resolution without a corresponding resolution in phantosmia symptoms.[6]

Medical management of phantosmia lacks large clinical trial evidence and no consensus exists regarding optimal treatment. However, medical therapy of phantosmia may be directed to the underlying etiology, such as anti-epileptic therapy for olfactory hallucinations associated with focal epilepsy[7,8] or prophylactic migraine medications for migraine-associated phantosmia.[6,7] There is some evidence that the distinction between peripheral phantosmia (a dysfunction at the level of the olfactory receptors and neurons) and central phantosmia (a dysfunction of the cortical olfactory pathways) may help guide therapy in that medical therapy is more likely to fail in peripheral phantosmia.[1,3]

Olfactory training in which patients sniff numerous scents representing major odor categories[9] has been discussed as a potential therapy for phantosmia.[9–11] A retrospective cohort study of 153 patients with post-infectious olfactory dysfunction undergoing olfactory training therapy found that the presence of phantosmia failed to be associated with clinically relevant improvement in olfactory function, but this only points away from phantosmia being a positive predictive factor and does not elucidate whether olfactory training may be helpful for phantosmia itself in some patients.[12] No clinical trials have been performed on this subject.

Table IX-40. Studies investigating medical management of phantosmia

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Majumdar et al[4]	2003	4	Case reports	Sodium Valpoate or Phenytoin Sodium (n = 2)	Subjective improvement (at 3.5 y)	No analysis. Symptom resolution.

Landis et al[2]	2010	4	Cohort	Observation (n = 44)	Subjective improvement (at mean 6 y)	Phantosmia symptoms: disappeared in 14 (32%), improved in 11 (25%), remained the same in 17 (39%), worsened in 2 (5%). No association with gender, TDI score
Coleman et al[6]	2011	4	Cohort	Topirimate, verapamil, nortriptyline, gabapentin (n = 14)	Subjective improvement (at 30 mo)	Phantosmia symptoms: Improvement in 9/14 patients, all patients with headache resolution also had phantosmia resolution
Leopold et al[5]	2013	4	Cohort	Topical cocaine (n = 6)	Subjective improvement (at 19 mo)	Phantosmia symptoms: transient resolution in 5/6 patients for hours to days, 1/6 patient improved for 6 weeks. Phantosmia returned in all patients.
Morrissey et al[3]	2016	4	Cohort	Haloperidol for 3 mo (n = 5); Olfactory mucosa excision for failures (n = 3)	Subjective improvement (at 18 mo to 5 y)	Resolution of phantosmia in all patients, include 2/5 with haloperidol alone and 3/5 with surgery.
Liu et al[12]	2020	4	Cohort	Olfactory training therapy (n = 43)	Sniffin' Sticks test (at mean 26 weeks)	Presence of phantosmia failed to be associated with clinically relevant improvement in olfactory function
[n = number, y = years, mo = months, odor threshold (T), odor discrimination (D), and odor identification (I)]						

Aggregate Grade of Evidence for Medical Management of Phantosmia: C (Level 4: 6 studies).

Of note, this evidence grade is based on the studies listed in the above table. However, due to the high variation in treatment options, a reliable evidence grade is difficult to determine. Based on the available evidence, it appears that trialing these different medical therapies for recalcitrant phantosmia, under careful follow-up and monitoring, could be an option based on balance of benefit and harm.

SECTION: XI. Management

G. Phantosmia/parosmia treatment

2. Surgical treatment options

The majority of patients with qualitative olfactory dysfunction will symptomatically improve or have resolution of symptoms with appropriate medical therapy or observation alone.[1–3] Therefore, watchful waiting or trials of different medical therapy are the first-line treatment recommendation. Surgical intervention is not recommended as a first line therapy and should

only be considered if patients fail multiple trials of medical therapy and symptoms are distressing enough to be life-threatening (unfortunately in rare cases, phantosmia and parosmia can lead to suicidal ideation).

There are case reports of olfactory nerve/bulb resection for long-lasting phantosmia/parosmia.[4–6] These procedures not only result in permanent anosmia, but also come with the potential risks of a skull base defect and need for repair and are therefore not recommended unless as a last resort.

An early case report by Leopold et al. details findings from the first unilateral endoscopic intranasal excision of the olfactory epithelium in a patient with long-lasting phantosmia.[7] Phantosmia initially resolved after excision of the olfactory epithelium and her olfactory ability returned post-operatively. Late follow-up revealed some return of phantosmia.

A recent systematic review by Saltagi et al[8] looked at both medical and surgical management of long-lasting phantosmia. In the two surgical studies, all patients (n=11) underwent endoscopic intranasal excision of the olfactory epithelium in the involved nostrils.[9,10] Postoperatively, phantosmia resolved in 10/11 patients. Of the 8 patients included in the Leopold et al[9] study, 2 underwent bilateral surgery and 4 underwent repeat surgery for persistent symptoms. Olfactory function was unchanged in 5 of the operated nostrils, decreased in 3 and improved in 2. All patients included in the Morrissey et al[10] study (n=3) developed anosmia post-operatively. There were no post-operative cerebrospinal fluid (CSF) leaks. Of note, an indication for surgery in both studies was the ability to abort the phantom smell with anesthetization of the involved nostril. Although initial success rates with surgical excision of the olfactory mucosa are relatively good, late follow-up is lacking. Additionally, there are serious risks of worsening olfactory function and CSF leak, so should only be performed by surgeons who routinely perform CSF leak repair.

A recent case report published in August 2020 by Liu et al,[11] details a novel surgical treatment in a patient with long-lasting peripheral parosmia. The olfactory cleft was blocked by creating intranasal adhesions. The patient had resolution of parosmia postoperatively and no recurrence at 2 year follow up. The patient did have resulting anosmia. The procedure has not been validated and therefore cannot be recommended at this time.

Table IX-42. Phantosmia/Parosmia Surgical Treatment Options						
Study	Year	LOE (1 to 5)	Study Design	Study Groups	Clinical Endpoint	Conclusion
Liu et al[11]	2020	4	Case report	Patient with peripheral parosmia underwent olfactory cleft blocking, n=1	1. Resolution of parosmia 2. Pre- and post-operative olfactory function	Olfactory cleft blocking procedure is a novel, simple, safe and effective procedure for patients with long-term peripheral parosmia
Saltagi et al[8]	2018	4	Systematic review of retrospective case series	Patients with phantosmia undergoing medical and/or surgical treatment	Resolution of phantosmia	2 studies looking at surgical intervention were included [9, 10]. n=11. 10/11 patients had resolution of symptoms. Given the lack of strong evidence to date and risks associated with olfactory cleft procedures, surgery should not be viewed as a definitive clinical tool but rather as an option within the research paradigm for managing phantosmia.
Morrissey et al[10]	2016	4	Retrospective case series	Patients with peripheral phantosmia who failed a 3-month trial of haloperidol underwent endoscopic resection of olfactory neuroepithelium, n=3	Resolution of phantosmia	All patients had resolution of phantosmia after surgical resection of olfactory neuroepithelium. No patients experienced a CSF leak. All experienced unilateral anosmia on the operated side.
Leopold et al[9]	2002	4	Retrospective case series	Patients with phantosmia underwent intranasal excision of olfactory epithelium, n=8	1. Resolution of phantosmia 2. Pre- and post-operative	7/ 8 patients had complete and permanent resolution of their phantosmia. Surgical excision is an effective and safe

					olfactory function 3. Histologic findings	method to relieve phantosmia, but the procedure is technically and carries the risk of CSF leak.
Leopold et al[7]	1991	4	Case report	Patient with unilateral phantosmia underwent intranasal excision of olfactory epithelium, n=1	1. Resolution of phantosmia 2. Pre- and post-operative olfactory function 3. Histologic findings	Resolution of phantosmia and return of olfactory function
CSF = cerebrospinal fluid						

Surgical Intervention for Parosmia/Phantosmia

Aggregate Grade of Evidence: D (Level 4: 5 studies)

Benefit: Given the lack of strong evidence in the literature, a definitive benefit of surgical intervention cannot be supported at this time except in extremely rare cases of life threatening parosmia/phantosmia.

Harm: There are risks of worsening olfactory function and CSF leak with surgical excision of olfactory mucosa. The surgery is technically challenging and should only be performed by experts in the field.

Cost: There are no studies investigating the costs of surgical treatment of phantosmia.

Benefits-Harm assessment: The risks of olfactory cleft surgery outweigh the benefits at this time unless in the hands of an expert. Given that most cases tend to resolve with time, watchful waiting and medical management should always be recommended first.

Value Judgements: Surgical intervention should only be considered in very severe cases of phantosmia that are life threatening and do not respond to multiple trials of different medical therapies. This technically challenging surgery should only be performed by experts in the field.

Policy level: Option for rare cases

Intervention: Surgical intervention for phantosmia is not recommended at this time, except in extremely rare cases. Referral to an expert in this field can be considered in cases that do not resolve with time, have failed multiple trials of medical therapy, and are life threatening.

SECTION X: Special Considerations

A. Delay in initiating treatment may be detrimental to potential recovery

In certain circumstances, such as in the case of a child presenting with congenital anosmia associated with congenital hypogonatropic hypogonadism (CHH), also known as Kallman syndrome, timely diagnosis and treatment could change the course of the patient's life.[1]

In other forms of smell loss, the timing of diagnosis and treatment also matters with regard to the patient's chance of regaining normal smelling ability. In clinical trials evaluating intervention to help those with olfactory loss, the duration of loss was a significant factor in how well patients responded to treatment.[2–4] Additionally, in functional brain mapping and connectivity studies, chronic peripheral olfactory loss led to wide ranging changes in functional connectivity throughout the brain, both in olfactory specific cortices but also in recruiting other neural networks.[5,6] Although it appears clear that the sooner an intervention takes place the more likely the patient will be able to benefit from it, the exact answer as to how long is too long before no more improvement is possible, is not currently known. This is an important question for our field to answer, as it would lead to more accurate counseling of our patients regarding prognosis, as well as improved allocation of clinical time and resources to those that we know we can help.

SECTION X: Special Considerations

B. Multiple hit hypothesis

In specific forms of olfactory loss, such as that associated with CRS, there are particular risk factors that can predispose a patient to developing more permanent or longer lasting olfactory dysfunction. We know that polyp status, asthma, diabetes and age are all independent predictors of this.[1] We also know that in addition to age, male patients, and patients with poor general health (including histories of asthma, cancer, cardiovascular disease, nasal disease, and obesity), less physical activity, a history of cigarette smoking, lower family income, exposures to environmental toxicants, heavy drinking behavior, poorer education, being an ethnic minority, and those with lower cognitive function, are more likely to suffer from olfactory loss from other etiologies.[2,3] These types of predisposing or predictive factors appear to support a multiple hit hypothesis, by which sequential inflammatory insults or insults related to decreased blood flow, and the associated decrease in oxygenation and nutrition, to the structures within the olfactory system, may lead to olfactory dysfunction that is more permanent and difficult to recover from. However, we are lacking any real data demonstrating the weight of each of these factors relative to one another for each etiology of smell dysfunction, and why some patients with

many of these comorbidities and risk factors continue to have normal smelling ability. This is an area for potential future research.

SECTION X: Special Considerations
C. Inherent predisposition of cranial nerve dysfunction when exposed to viruses

Viruses such as influenza, measles, mumps, rubella, varicella-zoster, and herpes-simplex virus infection, play a crucial role in causing cranial nerve dysfunction, including post-viral olfactory loss, trigeminal chemosensory dysfunction, sudden sensorineural hearing loss and vocal fold paresis/paralysis.[1,2] Pathophysiology of other cranial neuropathies has been shown to involve neuroinflammation, apoptosis, and destruction of neurons, which is similar to post-viral olfactory loss in that it has been documented that neuroinflammation of the olfactory nerves or epithelium leads to neuronal injury and morphological alteration of both the olfactory bulb and cortex.[1,3–5]

Jitaroon et al[6] reported higher incidence of cranial neuropathies in post-viral olfactory loss patients than in a control group. Additionally, a family history of neurologic diseases, such as dementia, Alzheimer's disease, and stroke, was also shown to be a potential risk factor of having both post-viral olfactory loss and other cranial neuropathies. When considering these neurologic associations, there may be an inherent genetic vulnerability or susceptibility to neuropathy in some individuals or families. Theories as to what would cause this susceptibility range from a genetic propensity to mount an aggressive localized or systemic inflammatory response to a viral attack or other underlying genetic mechanism, versus a common familial exposure to environmental risk factors. More research in this area would help us understand potential risk factors that have not previously been explored.

SECTION X: Special Considerations
D. Discussion of protective and supportive measures
1. Control of environmental and food related risks

Patients with smell loss should be counseled regarding safety issues associated with olfactory dysfunction. Surveys of patients with hyposmia or anosmia found that the degree of olfactory impairment correlated with the frequency of hazardous events associated with loss of smell.

These incidents included burning of food or pots and pans associated with cooking, inability to smell a fire or smoke, failure to smell a natural gas leak, or ingestion of spoiled food or toxic substances.[1,2] The percentage of patients who reported experiencing a hazardous event related to their smell loss ranged from 22-24% for those with mild hyposmia to 39-45% with anosmia, three times the rate of those with normosmia.[1,2] In addition, patients with impaired olfaction reported concern related to these safety issues which impacted their quality of life.[3] Olfactory testing was included in the United States National Health and Nutrition Examination Survey (NHANES) of adults; of those age 70 years and older, 20.3% were unable to correctly identify smoke and 31.3% failed to correctly identify natural gas odor.[4]

Patient should receive information regarding their risks for hazardous events related to their smell loss as well as recommendations for safety measures. Family members or housemates should be made aware of the limitations of the patient's ability to smell or detect hazardous odors or spoiled food in order to assist with safety concerns. Smoke detectors should be installed and tested twice a year throughout the house as well as near the kitchen due to the risk of burning food or fires. For those with natural gas or propane in the home, gas leak alarms should be installed in furnace rooms, near fireplaces and near gas stoves, as someone with anosmia would be unable to smell the mercaptan additive in the gas. These gas leak alarms differ from carbon monoxide alarms, which will not detect a gas leak. Finally, those with anosmia or severe hyposmia should be aware of the risk of ingested spoiled food and utilize expiration dates or label foods with dates when storing them.

SECTION X: Special Considerations
D. Discussion of protective and supportive measures
2. Nutritional monitoring

Binge eating disorder (BED) is the most prevalent eating disorder with 2-4% of the general population afflicted. While some patients meet criteria of obesity, attacks of binge eating might also occur in patients with anorexia nervosa resulting in weight loss or that are able to maintain a normal weight.[1]

Sensory influences on food choices may still be underrated despite the sense of smell playing a priming role in flavor perception.[2,3] Several additional eating disorders have been associated with altered olfactory capacities.[4,5] Alternatively, olfactory dysfunction (OD) may alter eating behaviors and food appreciation.[6–8] In subjects with food avoidance, this disorder might be sensory-related, specifically to aspects of flavor perception (including smell, taste, texture, and color).[9] While sensory-specific satiety does not seem to be different in subjects with OD,[10] altered eating behaviors in OD may include distortion of food intensity,[8] decreased pleasure in novel food,[11] over-salting[12] and tendency to spicy dishes.[7] Weight gain has been reported for patients with anosmia, in contrast to weight loss more likely in patients with hyposmia.[13]

Further research on eating alterations as a consequence of OD is needed, utilizing validated tools. Although a questionnaire-based score has been proposed in OD research for detection of eating alterations with excellent reliability,[7,14] future investigators should consider methods used in larger populations regardless of chemosensory function.[15,16] Beside these "assessment" aspects, monitoring and counseling will need standardization. At this stage, patient counseling with dietary diaries on a daily basis for the duration of four weeks after first consultation regarding OD should be recommended. Moreover, it is suggested to at least document weight loss or gain.

Patients with smell loss should be advised to control salt intake, and monitoring through general practitioners (e.g., blood pressure, renal function) should be recommended. Although it has been shown that many patients will learn to adjust and cope with OD in the long run,[17] intermittent nutritive counseling by experts should be considered. Beyond monitoring, flavor enhancement of food may play a role in the future to improve palatability and/or intake of dishes in patients with chemosensory complaints.[18] The importance of physical activity, sufficient hydration and regular sleep should be part of patient management and counseling. Lastly, in case of a specific eating disorder accompanying OD, beside chemosensoric counseling, strategies that have shown to be effective in this selected field may be applicable and should be considered, such as cognitive behavioral therapy or psychotherapy in BED.[1]

SECTION X: Special Considerations
D. Discussion of protective and supportive measures
3. Counseling or therapy for psychologic effects

While a number of studies exist evaluating medical treatment (for a review, see Boesveldt et al[1]), to our knowledge no information on psychological interventions in the context of olfactory disorders is yet available. In view of the negative side effects of the sensory loss on emotional state and general well-being reported by affected patients (see section *VI. The Individual Burden of Olfactory Dysfunction*), this seems striking. The following paragraph thus shortly elucidates available treatment approaches with regard to the psychological effects of olfactory dysfunction.

Psychological interventions should focus on three aspects in order to enable the best suitable therapeutic approach. First, as in every psychotherapeutic routine, a detailed diagnosis should be done assessing subjective suffering and impairments of categorical life areas in order to capture different aspects of mental health. Therefore, a standardized diagnostic interview (e.g, SKID[2]) can be carried out. The individual diagnoses then should be treated with evidence based psychotherapeutic interventions (e.g., for depressive disorders[3]). Besides these management strategies, particular effects of the olfactory loss on mental state have to be examined. The subjective importance of olfaction has to be explored in detail in order to i) evaluate the extent of individual impairment and to ii) develop suitable strategies for detachment processes, e.g., gaining acceptance of the situation. The individual significance of olfaction can be assessed by a questionnaire,[4] which comprises application, association and consequences of olfaction and thus gains insight in affected life areas. In that context, it is important to carefully explore and modify coping strategies[4] as currently used by the patient in order to ensure adaptive adjustment to the deficits.[6] Many olfactory disorder patients exhibit adequate emotionally focused coping strategies, e.g, "trying to make the best of the situation" or "comparing one's problems with those who are worse off,"[5,7] as well as gradually attributing less importance to the sense of smell in their daily life.[8] This allows emotional detachment, which in turn serves maintenance of mental well-being despite the sensory loss.[9] In general, strategies to enable emotional acceptance, e.g, practicing mindfulness,[10,11] are a valuable tool

in order to sustain life quality and self-esteem.[12–14] Beyond that, communication strategies, e.g., how willing the patient is to talk about the loss, should be targeted, as this has been shown to ease individual burden and help patients deal with the deficit.[15]

SECTION XI: Summary of Knowledge Gaps and Research Opportunities

A. Etiology

1. Better delineate etiologies – many patients still characterized as idiopathic

Current classification of olfactory dysfunction is mainly based on the underlying etiology, such as rhinosinusitis, upper respiratory viral infection and head trauma. If the cause of olfactory dysfunction cannot be specified, olfactory dysfunction is classified as idiopathic.[1] The diagnostic modalities for olfactory dysfunction include careful history taking, endoscopic inspection of the nasal cavity, CT and MR imaging, and olfactory tests. Previous studies have demonstrated such diagnostic methods are useful to differentiate idiopathic olfactory loss from the olfactory dysfunction of specific causes. For example, CT imaging is useful for the diagnosis of olfactory dysfunction associated with rhinosinusitis.[2,3] MRI is useful to diagnose olfactory dysfunction caused by skull base disease.[4] MRI is also useful to evaluate olfactory sulcus depth, olfactory bulb volume, and bulb and nerve morphologies, which may provide diagnostic information on different etiologies of olfactory dysfunction.[5] However, it is sometimes difficult to exclude the possibility of olfactory dysfunction due to airflow limitation related to mild rhinosinusitis, previous mild head trauma, otherwise asymptomatic viral infection, and early neurodegenerative diseases, from the “idiopathic” olfactory loss category - even using these modalities.

It has been reported that a short course of oral steroid administration is useful to differentiate conductive olfactory loss, however we know this may help with sensorineural loss as well.[6] Future improvement in testing methods using new technologies such as radioisotope transport,[7] biochemical analysis of olfactory mucus,[8,9] or technologies currently in development, may contribute to the establishment of improved classification of olfactory dysfunction based on more accurate pathophysiology.

SECTION XI: Summary of Knowledge Gaps and Research Opportunities

A. Etiology

2. Relative Susceptibility and Underlying Mechanisms

While the variety of insults causing olfactory dysfunction are well categorized, different individual responses remain poorly understood.[1] Among the most common causes of olfactory dysfunction are rhinosinusitis, head trauma, presbyosmia, and post-viral olfactory disorder. If nasal obstruction is excluded, mechanisms may be considered to be sensorineural, but pathogenesis can vary widely. For instance, there is evidence for "wear-and-tear" changes or patches of respiratory metaplasia occurring in the olfactory epithelium in presbyosmia,[2,3] but related pathology in the olfactory bulb or cortex may be contributory.[4] Also, mechanisms underlying respiratory metaplasia are not clear: is this due to failed epithelial reconstitution, or neurogenic exhaustion, and is it permanent? Analogous questions occur with post-viral loss, which is associated with a large number of viruses, impacting different cell populations or triggering varying immune responses. SARS-CoV-2 poses additional questions, as sustentacular cells are the target,[5] and the clinical picture ranges from no symptoms to fatal disease, with many patients exhibiting brief anosmia and others remaining hyposmic or parosmic longer term. The range of pathogens or injuries, coupled with the specific cellular targets and varying host immune responses pose a challenge for understanding the degree and duration of sensory dysfunction, and for developing the appropriate therapeutic approaches. Research into these various mechanisms by which individuals become hyposmic will better delineate why some appear to be more susceptible than others to the same insult.

<u>Knowledge gaps – We need better animal models and understanding of what happens on a cellular level and olfactory system level in non-sinonasal inflammation related etiologies of olfactory dysfunction</u>

Rodent models have provided a wealth of knowledge regarding olfaction, yet gaps remain. Disorders thought to result from direct damage to the olfactory epithelium have been modeled in rodents using intranasal chemicals or systemic drugs.[6,7] Following chemical damage, olfactory epithelial reconstitution and axon projection to the olfactory bulbs may be assessed. Olfactory bulbectomy may model central injuries marked by olfactory neuron degeneration, and weight drop or blast injury models have also been useful for post-head trauma olfactory modelling.[8] Genetic models to test cell type-specific gene knock out, to target toxins to specific cell types, or to induce ciliopathy may test gene function or model certain diseases. For instance, anosmia is a hallmark of ciliopathy disorders, since olfactory receptors are expressed on the cilia membrane of olfactory neurons. Ciliopathy mice have permitted the successful testing of a viral gene therapy for a loss-of-function mutation in a cilia transport gene.[9] Nonetheless, better models for other disorders are needed to understand pathogenesis and to test therapies. Recent rodent viral infection models may improve understanding of classical post-viral olfactory disorder, and models directing expression of specific viral entry genes on cell populations of interest will help us understand aspects of hyposmia associated with the novel coronavirus.[10]

SECTION XI: Summary of Knowledge Gaps and Research Opportunities

B. Clinical Assessment

1. **How culture and literacy affect some psychophysical test results**
2. **Developing more clinically accessible, truly objective, quantitative tests**

As noted in the above document, there are hundreds of different psychophysical olfactory tests. While these tests have been invaluable in gaining quantitative measures to compare against patients' subjective complaints, there are some assumptions that are necessarily made when this type of testing occurs. Some smell tests have been adapted to different countries and cultures, so that the odors presented are familiar to patients, whereas some others have not.[1–5]

Above and beyond this is that when a test is given to a patient to self-administer, as many of these tests are in a busy clinical practice, an assumption of literacy has been made. While it is likely that the majority of patients in first world countries may be literate, shame and embarrassment will often prevent that important minority of patients from telling their

providers about their illiteracy, and would rather have an incorrect test result. It is also true that if these tests are to be truly utilized globally, many other countries do not have a high literacy rate.[6]

Development of simpler quantitative tests

Electro-olfactograms (EOG) and adapted electro-encephalograms (EEG) have long been utilized in the research setting to try and provide more olfactory data points that are free from subjective and situational influence.[7] However, once a provider finds themselves in the typical busy clinical setting of their practice, it becomes impractical based on time, equipment and space requirements to perform the type of tests that are currently established, regularly. This is a definite area of research which is ripe for development, and simpler yet universal quantitative testing is already being developed in some centers.[8]

SECTION XI: Summary of Knowledge Gaps and Research Opportunities

C. Management

1. Identify predictors of response to current and future therapeutic options

It would be useful for the management of patients with olfactory dysfunction if the efficacy of each treatment option offered to them could be predicted in advance. For example, the olfactory dysfunction associated with rhinosinusitis often responds to treatments directed at controlling that underlying inflammation, such as endoscopic sinus surgery (ESS) and steroid administration. These interventions are often effective, although even in this population patients must be counseled that there is no guarantee that they will regain their normal smelling ability, especially after a long duration of loss. In contrast, prior study has demonstrated that systemic steroid treatment is more effective in patients with sinonasal inflammatory related olfactory dysfunction compared to patients with idiopathic olfactory dysfunction, especially when comparing to patients with sinonasal disease with nasal polyps.[1] Other studies demonstrated that success of a trial of systemic steroids may serve to verify that the loss is indeed inflammatory,[2] and is a prognostic indicator for a significant benefit of a topical steroid therapy.[3] As for ESS, a duration of up to 4.5 years of self-reported smell loss has

been suggested as the cut-off point for recovery of smell following ESS.[4] A positive response to an intravenous olfactory test, absence of olfactory cleft lesions, female sex, and younger age were also identified as independent prognostic factors for better olfactory outcomes 3 months after ESS.[5]

In post-viral olfactory disorder (PVOD), multivariate analysis showed that younger age and residual olfactory function were significantly associated with better olfactory recovery.[6] A study in Japan showed that onset latency in the intravenous olfactory test may help predict when olfaction in patients with PVOD will improve.[7] On the other hand, posttraumatic or idiopathic olfactory dysfunction were significantly associated with less possibility of improvements compared to PVOD in patients with olfactory dysfunction receiving olfactory training.[8] Finally, there is a significant correlation between changes in olfactory function and initial measurement of the total olfactory bulb volume, with larger volumes relating to higher improvement of olfactory function, although this does not predict which therapeutic option is best for either group.[9]

A new methodology, radioisotope transport analysis, has demonstrated that high thallium migration from the nasal cavity to the olfactory bulb is significantly correlated with better prognosis in patients with olfactory dysfunction, suggesting that patients with intact olfactory nerve fibers could be selected using this imaging technique.[10]

SECTION XI: Summary of Knowledge Gaps and Research Opportunities
C. Management
2. A "cure" for all olfactory disorders

In all probability, there will not be a single cure for all etiologies of olfactory dysfunction. This is due to the fact that olfactory disorders are not one monolithic entity, but instead can be dissected into different fractions,[1] similar to what has been seen for many other disorders. For example, during the past years we have learned that inflammation of the nasal and sinus cavity is not uniform and that different forms of sinonasal disease respond differently to different treatments.[2] Stimulating regeneration of olfactory receptor neurons,[3] transplantation of olfactory mucosa and working to develop stem cell regeneration[4] or developing olfactory

implants[5] are excellent ideas but may have limited effects on central nervous system causes of olfactory disorders residing at the level of the olfactory bulb or the orbitofrontal cortex. Detailed recognition and specification of these different entities is necessary. Future studies on these numerous ideas for an olfactory cure should therefore be more precise in terms of the selection of study participants.

SECTION XI: Summary of Knowledge Gaps and Research Opportunities

C. Management

3. Increase public awareness of this disorder and its many implications

Increasing public awareness regarding the importance of olfactory function and olfactory dysfunction is significant in terms of empathy and sympathy for patients suffering with these disorders, as well as an improvement of the understanding of the sense of smell, its disorders and possible therapies for changes of the sense of smell. This has not happened to a significant extent in the past, although age-related olfactory loss is very frequent and approximately 5% of the general population have no functioning sense of smell.[1] This lack of awareness of olfactory dysfunction is probably related to many factors. For example, the gradual decrease of olfactory function with aging, or the lack of significance of the sense of smell for most work-related situations. However, the current global situation seems to be changing. One major driver appears to be COVID19, with sudden olfactory loss observed in a large number of (also younger) patients, and the appearance of very active organizations organized by people with chemosensory dysfunction like Fifth Sense[2] or Abscent[3] in the UK, the Smell and Taste Association of North America (STANA),[4] or Reuksmaakstoornis in the Netherlands.[5] Because public awareness drives political decisions and, in consequence, the amount of funding provided for research on the sense of smell, it is important that researchers in this field take advantage of this increasing awareness and also approach the public more broadly and more frequently to move forward our research missions and knowledge base in this area.

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ICAR Line 10

The Individual Burden of Olfactory Dysfunction

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The Individual Burden of Olfactory Dysfunction

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ICAR Line 14

Anatomic Description of Human/Mammalian Olfactory System and brief overview of synaptic transmission and relevant cortical structures

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ICAR Line 15

Anatomic Description of Human/Mammalian Olfactory System and brief overview of synaptic transmission and relevant cortical structures

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ICAR Line 18

Pathophysiology

A. Sinonasal Inflammatory Disease

(1) Basic underlying mechanisms

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ICAR Line 19

Pathophysiology

A. Sinonasal Inflammatory Disease

1) Related to CRS

a) In relation to phenotype (NP or no NP)

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ICAR Line 20

Pathophysiology

A. Sinonasal Inflammatory Disease

1) Related to CRS

a) In relation to endotype

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ICAR Line 21

Pathophysiology

A. Sinonasal Inflammatory Disease

2) Related to allergic rhinitis or chronic rhinitis

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ICAR Line 22

Pathophysiology

B. Post-Viral Loss

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ICAR Line 23

Pathophysiology

B. Post-Viral Loss

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C. Head trauma

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Pathophysiology

D. Related to toxin exposure, environmental or work-related

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ICAR Line 26

Pathophysiology

E. Related to medications, all possible (include general anesthetics and chemo drugs)

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ICAR Line 27
Pathophysiology
F. Post-XRT

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ICAR Line 28

Pathophysiology

G. Related to underlying systemic disease

1) Auto-immune

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ICAR Line 29

Pathophysiology

G. Related to underlying systemic disease

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ICAR Line 30

Pathophysiology

G. Related to underlying systemic disease

3) Endocrine related

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ICAR Line 31

Pathophysiology

G. Related to underlying systemic disease

4) Renal failure

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ICAR Line 32

Pathophysiology

H. Related to sinonasal or intracranial tumor

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ICAR Line 33

Pathophysiology

I. Related to increasing age

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ICAR Line 35

Pathophysiology

K. Related to other neurotransmitter disease states (depression, schizophrenia, autism, etc.)

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ICAR Line 36

Pathophysiology

L. Related to seizure activity, to migraine or other headache activity

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ICAR Line 38

Pathophysiology

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Pathophysiology
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ICAR Line 40

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O. Idiopathic

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ICAR Line 41

Evaluation and Diagnosis

A. H&P (History, Physical Exam including full CN exam, Nasal endoscopy)

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ICAR Line 42

Evaluation and Diagnosis

B. Imaging (CT/MRI/fMRI, etc.)

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C. Use of validated quantitative smell tests

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ICAR Line 44
Evaluation and Diagnosis
D. Use of validated survey QOL testing

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ICAR Line 45

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E. Measurement of cytokine/mucin levels

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ICAR Line 46

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F. Electro-olfactogram

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ICAR Line 46b
Evaluation and Diagnosis
F. Role of bloodwork/lab values

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ICAR Line 47

Evaluation and Diagnosis

G. Specific evaluation and workup for phantosmia

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Management
C. Treatment of underlying sinonasal inflammatory etiologies
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ICAR Line 53

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ICAR Line 52b

Management

F. If no underlying disease state to correct:

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ICAR Line 53b

Management
F. If no underlying disease state to correct:
2. Olfactory training

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ICAR Line 54

Management

F. If no underlying disease state to correct:

3. Intranasal sodium citrate

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ICAR Line 55

Management

F. If no underlying disease state to correct:

4. Vitamins and supplements

a. Omega3

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ICAR Line 56

Management

F. If no underlying disease state to correct:

4. Vitamins and supplements

b. Zinc

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ICAR Line 57

Management
F. If no underlying disease state to correct:
4. Vitamins and supplements
c. Alpha lipoic acid

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ICAR Line 58
Management
F. If no underlying disease state to correct:
4. Vitamins and supplements
d. Vitamin A

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ICAR Line 59
Management
F. If no underlying disease state to correct:

4. Vitamins and supplements

e. taki-shakuyaku-san

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ICAR Line 60

Management

F. If no underlying disease state to correct:

5. Minocycline

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ICAR Line 61

Management

F. If no underlying disease state to correct:
6. Theophylline

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ICAR Line 62
Management
F. If no underlying disease state to correct:
7. Intranasal insulin

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ICAR Line 63

Management

F. If no underlying disease state to correct:

8. Platelet rich plasma

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ICAR Line 64

Management

G. Phantosmia/parosmia treatment

1. Medical treatment options

1. Saltagi MZ, Rabbani CC, Ting JY, Higgins TS. Management of long-lasting phantosmia: a systematic review. *Int Forum Allergy Rhinol*. 2018; 8: 790- 796.
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ICAR Line 65

Management

G. Phantosmia/parosmia treatment

2. Surgical treatment options

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ICAR Line 66

Special Considerations

A. Detrimental effect in possible recovery from delay in initiating treatment

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ICAR Line 67

Special Considerations
B. Any evidence regarding subsequent inflammatory insults leading to worsened function? (Pre-disposed to more loss once the system has weakened?)

1. Schlosser RJ, Smith TL, Mace JC, et al. Factors driving olfactory loss in patients with chronic rhinosinusitis: a case control study. *Int Forum Allergy Rhinol*. 2020; 10: 7- 14.
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ICAR Line 68
Special Considerations
C. Inherent predisposition of cranial nerve dysfunction when exposed to viruses

1. Yao L, Yi X, Pinto JM, et al. Olfactory cortex and olfactory bulb volume alterations in patients with post-infectious olfactory loss. *Brain Imaging Behav*. 2018; 12: 1355- 1362.
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6. Jitaroon K, Wangworawut Y, Ma Y, Patel ZM. Evaluation of the incidence of other cranial neuropathies in patients with postviral olfactory loss. *JAMA Otolaryngology Head Neck Surg*. 2020; 146: 465- 470.

ICAR Line 69
Special Considerations
D. Discussion of protective and supportive measures
1. Control of environmental risks: carbon monoxide, smoke, natural gas detectors, inspecting dates on food before eating

1. Santos DV, Reiter ER, DiNardo LJ, Costanzo RM. Hazardous events associated with impaired olfactory function. *Arch Otolaryngol Head Neck Surg*. 2004; 130: 317- 319.**[REFERENCED IN SECTION 11]**
2. Pence TS, Reiter ER, DiNardo LJ, Costanzo RM. Risk factors for hazardous events in olfactory-impaired patients. *JAMA Otolaryngol Head Neck Surg*. 2014; 140: 951- 955. **[REFERENCED IN SECTION 11]**

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Special Considerations

D. Discussion of protective and supportive measures

2. Keeping track of nutrition in cases of food avoidance or binge eating, (over-salting, over-sweetening, weight loss, etc.)

1. Berner LA, Winter SR, Matheson BE, Benson L, Lowe MR. Behind binge eating: A review of food-specific adaptations of neurocognitive and neuroimaging tasks. *Physiol Behav*. 2017; 176: 59- 70.
2. McCrickerd K, Forde CG. Sensory influences on food intake control: Moving beyond palatability. *Obes Rev*. 2016; 17: 18- 29.
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14. Besser G, Oswald MM, Liu DT, Renner B, Mueller CA. Flavor education and training in olfactory dysfunction: A pilot study. *Eur Arch Otorhinolaryngol*. 2020; 277: 1987- 1994.

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Special Considerations
D. Discussion of protective and supportive measures
3. Counseling or therapy for psychologic effects, etc.

1. Boesveldt S, Postma EM, Boak D, et al. Anosmia—a clinical review. *Chem Senses*. 2017; 42: 513- 523. **[USED IN SECTION 6/7]**
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ICAR Line 73

Summary of Knowledge Gaps and Research Opportunities

A. Etiology

1. Better delineate etiologies – many patients still characterized as idiopathic

1. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinol Suppl*. 2017; 54: 1- 30. **[REFERENCE USED IN SECTION 6 AND 7.]**
2. Mueller C, Temmel AF, Toth J, et al. Computed tomography scans in the evaluation of patients with olfactory dysfunction. *Am J Rhinol*. 2006; 20: 109- 12.
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6. Seiden AM, Duncan HJ. The diagnosis of a conductive olfactory loss. *Laryngoscope*. 2001; 111: 9-14. **[REFERENCE LISTED IN SECTION 18]**
7. Shiga H, Taki J, Okuda K, et al. Prognostic value of olfactory nerve damage measured with thallium-based olfactory imaging in patients with idiopathic olfactory dysfunction. *Sci Rep*. 2017; 7: 3581.
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ICAR Line 74 and 75

Summary of Knowledge Gaps and Research Opportunities

A. Etiology

2. Why are some people more susceptible to this than others from same insult?

3. Need better animal models and understanding of what happens on a cellular level and olfactory system level in non-sinonasal inflammation related etiologies of olfactory dysfunction

1. Doty RL. A review of olfactory dysfunctions in man. *Am J Otolaryngol.* 1979; 1: 57- 79.
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ICAR Line 76 and 77

Summary of Knowledge Gaps and Research Opportunities

B. Clinical Assessment

1. How culture and ability to read may affect some quantitative test results

2. Developing more clinically accessible quantitative test that are more truly "objective"

1. Fornazieri MA, Doty RL, Santos CA, et al. A new cultural adaptation of the University of Pennsylvania Smell Identification Test. *Clinics (Sao Paulo).* 2013; 68: 65- 68.
2. Balungwe P, Huart C, Matanda R, et al. Adaptation of the Sniffin' Sticks test in South-Kivu. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2020; 137: 467- 471.
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ICAR Line 78

Summary of Knowledge Gaps and Research Opportunities

C. Management

1. Better identify predictors of response for the therapies that have some efficacy

1. Schriever VA, Merkonidis C, Gupta N, et al. Treatment of smell loss with systemic methylprednisolone. *Rhinology*. 2012; 50: 284- 289.
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7. Horikiri K, Kikuta S, Kanaya K, et al. Intravenous olfactory test latency correlates with improvement in post-infectious olfactory dysfunction. *Acta Otolaryngol*. 2017; 137: 1083- 1089.
8. Ogawa T, Nakamura K, Yamamoto S, et al. Recovery over time and prognostic factors in treated patients with post-infectious olfactory dysfunction: A retrospective study. *Ann Otol Rhinol Laryngol*. 2020; 129: 977- 982.
9. Rombaux P, Huart C, Deggouj N, et al. Prognostic value of olfactory bulb volume measurement for recovery in postinfectious and posttraumatic olfactory loss. *Otolaryngol Head Neck Surg*. 2012; 147: 1136- 1141.
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ICAR Line 79

Summary of Knowledge Gaps and Research Opportunities
C. Management
2. Work towards a therapy that can "cure" all olfactory dysfunction

1. Whitcroft KL, Hummel T. Clinical diagnosis and current management strategies for olfactory dysfunction: A review. *JAMA Otolaryngol Head Neck Surg*. 2019; 145: 846- 853.
2. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020; 58:1- 464.
3. Mainland JD, Barlow LA, Munger SD, et al. Identifying treatments for taste and smell disorders: Gaps and opportunities. *Chem Senses*. 2020; 45: 493- 502.
4. Kurtenbach S, Goss GM, Goncalves S, et al. Cell-based therapy restores olfactory function in an inducible model of hyposmia. *Stem Cell Reports*. 2019; 12: 1354- 1365.
5. Holbrook EH, Coelho DH. Cranial nerve stimulation for olfaction (cranial nerve 1). *Otolaryngol Clin North Am.* 2020; 53: 73 -85.

ICAR Line 80
Summary of Knowledge Gaps and Research Opportunities
C. Management
3. Increase public awareness of this disorder and its many implications

1. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinol Suppl*. 2017; 54: 1- 30. **[REFERENCE USED IN SECTION 6 AND 7.]**
2. Fifth Sense website. Accessed July 16, 2021. https://www.fifthsense.org.uk/
3. AbScent website. Accessed July 16, 2021. https://abscent.org/
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