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REVIEW ARTICLE

International consensus statement on 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 past two decades, with an exponential rise in the past 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 on Allergy and Rhinology: Olfaction (ICAR:O).

Methods: Using previously described methodology, specific topics were developed relating to olfaction. Each topic was assigned a literature review, evidence-based review, or evidence-based review with recommendations 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 nearly 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.

KEYWORDS
anosmia, evidence-based medicine, hyposmia, loss of smell, olfaction, olfactory dysfunction, olfactory loss, parosmia, phantosmia, systematic review

List of abbreviations

AAPSCQIM	American Academy of Pediatrics Steering Committee on Quality Improvement and Managements
$A\beta_{1\text{-}}42$	Beta-amyloid
ACE2	Angiotensin Converting Enzyme 2
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease
ADD	Alzheimer's disease dementia
ADHD	Attention deficit/hyperactivity disorder
AERD	Aspirin-Exacerbated Respiratory Disease
AHSP	Appetite, Hunger and Sensory perception
ADLB	Alzheimer's dementia with Lewy bodies
AES	Apathy Evaluation Scale
ALS	Amyotrophic lateral sclerosis
ALS-N	ALS with normal cognition
AMG	Amygdala
aMCI	amnestic mild cognitive impairment
AN	Animal naming test or Anorexia Nervosa
AR	Allergic rhinitis
AROMA	Affordable, Rapid, Olfactory Measurement Array
ART	Akinetic-Rigid Type
ASA	Aspirin Desensitization Therapy
AS-Cog	Assessment Scale-Cognition
ASD	Autism Spectrum Disorder
α-syn	alpha-synuclein protein
BAST-24	Barcelona Smell Test
BAI	Beck Anxiety Inventory
BBB	Blood Brain Barrier
BD	Behcet's disease
BDI	Beck Depression Inventory

BED	Binge Easting Disorder
bFGF	basic fibroblast growth factor
BICAMS	The Brief International Cognitive Assessment for MS
BMI	Body Mass Index
BMS	burning mouth syndrome
BNT	Boston Naming Test
BOLD	Blood oxygen level-dependent signal
BOMCT	Blessed Orientation Memory Concentration Test
BPD	Bipolar Disorder
BSG	basigin
B-SIT®	Brief Smell Identification Test (also known as the Cross-Cultural Smell Identification Test or CC-SIT)
BTT	Butanol threshold test
BVMT	Brief Visuospatial Memory Test
CA	Congenital anosmia
CAMCOG	Cambridge Examination for Mental Disorders in the Elderly
cAMP	cyclic adenosine monophosphate
CASI	Cognitive Abilities Screening Instrument
CCCRC	Connecticut Clinical Chemosensory Research Center test
CCL	chemokine ligand
CCR	chemokine receptor
CD	Cognitive decline
CDKN2A/P16INK4a	Cyclin-dependent kinase inhibitor 2A/P16
CFD	computational fluid dynamics
cGMP	cyclic guanine monophosphate
ChE	Cholinesterase
CHH	congenital hypogonatropic hypogonadism
CI	Cognitive impairment
CLC	Charcot Leyden crystal protein
CN I	Cranial nerve one
CNS	Central Nervous System
COT	Classic olfactory training
COMB	Combination
COVID-19	coronavirus disease 2019
COWAT	Controlled Oral Word Association Test
CPG	Clinical Practice Guideline
CR	Chronic Rhinitis
CRP	C-reactive protein
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSF	Cerebrospinal fluid
CSIT	40-item Chinese Smell Identification Test
CSQ	Chemosensory questionnaire
CT	Computerized tomography
CVLT II	California Verbal Learning Test-II
CXCL	chemokine (C-X-C motif) ligand
D	CFL: Category Fluency: Discrimination
DAT	Dopamine transporter
DHA	docosahexanoic acid
DISC	Discrimination
DIP	Drug-induced Parkinsonism
DLB	Dementia with Lewy bodies
DM	Diabetes mellitus
DMT	disease-modifying therapy
DODT	Disseldorf Odour Discrimination Test
DRS	Dementia Rating Scale
DT	Detection threshold
DTI	Diffusion tensor imaging
EBM	Evidence Based Medicine
EBR	Evidence Based Review
EBRR	Evidence Based Review with Recommendations
ECP	Eosinophilic cationic protein
EDSS	Expanded Disability Status Scale
EEA	Endoscopic endonasal approach
EHLS	Epidemiology of Hearing Loss Study
EMBASE	Excerpta Medica database
EO-PD	Early-onset PD
EOG	Electro-olfactogram
ERP	Event-related potential
ETTH	Episodic tension type headache
ESS	Endoscopic sinus surgery
F	Female
FA	Fractional Anisotropy
FAB	Frontal Assessment Battery
FDA	Federal Drug Administration
FDG	^{18}F-2-fluoro-2-deoxy-D-glucose
FFQ	Food-Frequency Questionnaire
FG	Fusiform gyrus
FH	Family history
fMRI	Functional magnetic resonance imaging
FP	Fluticasone propionate
FTD	Frontotemporal dementia
FTG	Fusiform gyrus
FTG-PET	Positron emission tomography using the radiopharmaceutical fluorodeoxyglucose
GAD-7	Generalized Anxiety Disorder

GCS	Glasgow Coma Scale
GM	Gray matter
GM-CSF	Granulocyte monocyte-colony stimulating factor
GPA	Granulomatosis with Polyangiitis
HAND	HIV-associated neurocognitive disorders
HARS	Hamilton Anxiety Rating Scale
HBC	Horizontal basal cells
HC	Healthy controls
HD	Huntington's disease
HDRS	Hamilton Depression Rating Scale
Hipp	Hippocampus
HLA	Human Leukocyte Antigen
HNC	Head and Neck Cancer
HRSL	Hyposmia Rating Scale
HRV	Heart rate variability
HWM	Heavy Weight Molecules
ICA	Isolated congenital anosmia
ICAR:O	International Consensus Statement on Allergy and Rhinology: Olfaction
ICD	Intracranial disease
ICHD	International Classification of Headache Disorders
ID	Identification
IFG	Inferior frontal gyrus
IFN-γ	interferon gamma
IgG4RD	Immunoglobulin G4 – related disease
IgE	Immunoglobulin E
IL	interleukin
ILB	Incidental Lewy Bodies
IMRT	Intensity-modulated radiotherapy
KS	Kallmann syndrome
LARK2	*Leucine-Rich Repeat Kinase* 2 gene
LASA	Longitudinal Aging Study Amsterdam
LCPUFA	long chain polyunsaturated fatty acids
LOE	Level of Evidence
LO-PD IMC	Information-Memory-Concentration Test for Late-onset PD
LOT-R	Life Orientation Test
LR	Literature Review
LS	Loneliness Scale
LWM	Light Weight Molecules
M	Male
M cells	Mitral cells
MA	Migraine with aura
MC	Mutation carrier
MCI	Mild cognitive impairment
MCID	Minimal clinically important difference Multi-Clinic Smell and Taste Questionnaire-Scandanavian (MCSTQ-Sc)
MczD	Mikulicz's disase
MD	Major depression
MDD	Major depressive disorder
MDI	Major depression inventory
MEDLINE	Medical Literature Analysis and Retrieval System Online
MFI	Modified Fatigue Impact
MG	Myasthenia gravis
MHC	Major Histocompatability Complex
MIBG	^{123}I-meta-iodobenzylguanidine
MITG	Middle/Inferior temporal gyri
MMSE	Mini-Mental State Examination
MO	Migraine without aura
MOA	Monoamine
MOCA	Montreal Cognitive Assessment
MP	Methylprednisolone
MPS	Mild Parkinsonian signs
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
MTC	Medial temporal cortex
MND	Motor neuron disease
MS	Multiple Sclerosis
MSSS	Multiple Sclerosis Severity Score
MTHFR	methyl tetra folate reductase enzyme mutation
MultD	Multiple cognitive domain
naMCI	non-amnestic mild cognitive impairment
N	Nuclear Factor
NAR	Non-Allergic Rhinitis
ND	Neurodegenerative disease
NDE	Plasma neuronal-derived exosome
NE	Normal elderly
NDE AB_{1-42}	Plasma neural-derived exosome amyloid beta peptide 42
NHANES	U.S. National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NO	Neuromyelitis optica
NOSE	Nasal obstruction symptom evaluation
NPC	Nasopharyngeal carcinoma
NPH	Normal pressure hydrocephalus
NR	Not reported
NRP1	neuropilin-1
NT	neurotransmitter

NSHAP	National Social Life, Health, and Aging Project
NVF	Nasal volume flow
OB	Olfactory Bulb
OBV	Olfactory bulb volume
OC	Olfactory cleft
OCD	Obsession-compulsive disorder
OCM	Odor confusion matrix
OD	Olfactory disorder/dysfunction
ODT	Odor Memory/Discrimination Test
OE	Olfactory Epithelium
OERP	Odor event-related potential
OET	Open Essence Test
OF	Olfactory Function
OFC	Orbitofrontal cortex
OFFE	Olfactory Function Field Exam
OLFACT-RL	Osmic Enterprises Olfactometer
ON	Odor naming test
OPM	Odor picture matching
OR	Olfactory receptor
ORS	Olfactory Reference Syndrome
OS	Olfactory sulcus
OSIT-J	Odor stick identification test for Japanese
OSL	Olfactory sulcus length
OSN	Olfactory sensory neuron
OT	Olfactory tract
P	precuneus
PASAT	Paced Auditory Serial Addition Test
PBT	Peanut Butter Test
PCC	Posterior cingulate cortex or post-central cortex
PCG	Postcentral gyrus
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PDG	Parkinson Dementia Complex of Guam
PDEI	Phosphodiesterase Inhibitor
PEA	Phenyl Ethyl Alcohol
PEMEC	phenylethylmethylethyl carbinol
PET	Positron Emission Tomography
PI	Post-infectious
PIB	11C-Pittsburgh Compound B
PIGD	Postural instability gait disorder
PIOD	Post-infectious olfactory disorder
PIT	Picture Identification Test
PIV3	Parainfluenza virus type 3
PNIF	Peak Nasal Inspiratory Flow
PMS	progressive multiple sclerosis PNIF –peak nasal inspiratory
PO	Post-operative
POC	Primary olfactory cortex
POEM	Percepts of Odor Episodic Memory olfactory battery
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	Platelet Rich Plasma
pSS	primary Sjogren's Syndrome
PST®	Pocket Smell Test
PT	Post-traumatic
PTA	posttraumatic amnesia
p-tau	phosphorylated tau protein
PVOD	Post-viral Olfactory Dysfunction
QOD	Questionnaire of olfactory deficits/disorders
QOD-NS	Questionnaire of olfactory disorders – negative statements
QOL	Olfactory-specific quality of life
RA	Rheumatoid arthritis
RBD	rapid eye movement sleep behavior disorder
RBDSQ	REM Sleep Behavior Disorder Screening Questionnaire
rCBF	Regional cerebral blood flow
RCT	Randomized Controlled Trial
RLS	Restless Leg Syndrome
ROC	receiver operating characteristic
RS	Rhinosinusitis
RSDI	Rhinosinusitis disability index
RRMS	Relapsing-remitting multiple sclerosis
RT	Radiation therapy or recognition threshold
SAD	Seasonal Affective Disorder
SARS-CoV-2	Severe acute respiratory syndrome – coronavirus - 2
SCD	Subjective cognitive decline
SCF	Stem cell factor
SCZ	Schizophrenia
SD	Signal detection
SDMT	Symbol Digit Modalities Test
SDOIT	San Diego Odor Identification Test
SF-8	Short Form Health Survey-8
SF-36	Short Form Health Survey-36
SLE	Systemic Lupus Erythematosis
SND	sinonasal disease
SNOT-22	Sino-Nasal Outcome Test
SOIT	Scandinavian Odor Identification Test
SPECT	Single photon emission tomography
SPL	Superior parietal lobe
SPM	Sensory Processing Measure
SRT	Selective Reminding Test

SS	Sjogren's syndrome (in autoimmune context)
SS	Sniffin' Sticks (in olfactory test context); SS-ID – Identification; SS-T – Threshold; SS-D – Discrimination; SS-TDI: combined T, D & ID
STT	Smell threshold test
S&S-T	Snap & Sniff® threshold test
S&T	Smell and taste
SWLS	Satisfaction with Life Scale
Sx	Symptom
T	Threshold
T cells	Tufted cells
TBI	Traumatic brain injury
TD	Tremor dominant
THC	Δ^9-tetrahydrocannabinol
TLE	Temporal lobe epilepsy
TNF-α	Tumor necrosis factor alpha
TOIT	Thai Odor Identification Test
TSPO	18kDa translocator protein
TSS	Toki-shakuyaku-san
t-tau	total tau protein
TWSNOT-22	Taiwanese version of the 22-item Sino-Nasal Outcome Test
T&T	Toyota and Takagi olfactometer
UPDRS	Unified Parkinson's Disease Rating Scale
UPSIT®	University of Pennsylvania Smell Identification Test
URI	Upper Respiratory Infection
VAS	visual analogue scale
VD	Vascular dementia
W	week
WM	White matter
WNL	Within normal limits

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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 21st 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 (OE), olfactory bulb (OB), and olfactory 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 and complexity of study design over the 2 decades that have followed, peaking within the past year as the COVID-19 pandemic brought loss of smell and taste to the forefront of international importance and recognition.[2,3]

In the many decades before Axel and Buck’s publication, articles 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 2325 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 document is to summarize the best external evidence to provide practitioners the means to practice evidence-based medicine when diagnosing and treating these patients. As is the case among 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 an inherently multidisciplinary field, we endeavored to include authors from a wide array of expertise to ensure the highest and most insightful coverage of the subject. More than 50 international authors undertook a structured review of the literature in nearly 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 and not a meta-analysis. In fact, because of 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 by the wide variation in treatment methodology that exists around the globe for these patients. When we do not have high-level evidence on which to base our practice decisions, it is in our best interest as clinicians and scientists to identify the gaps in our current knowledge and attempt to design and perform 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 a 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 that may affect the evaluation and treatment of their specific olfactory loss or dysfunction. Finally, the idea of creating a document such as this, which strives to gather and review all of 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

A | Topic Development

All ICAR documents follow the formula of literature review described in 2011 by Rudmik and Smith,[7] utilizing their method of iterative evidence-based review (EBR) with recommendations (EBRRs). The literature was analyzed, assessed for level of evidence (LOE), 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, an EBR, or an 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 Library 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 LOE. When these did not exist, observational studies were then identified. Reference lists of all identified studies were examined to ensure that all relevant studies were captured. If the authors felt as though a non–English language study should be included in the review, the article 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 (OD). The evidence for this topic was rapidly evolving during the

TABLE II.A.1 Levels of evidence

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

[a]The level may be graded down on the basis of study design, inconsistency between studies, indirectness of evidence, or imprecision, or because the absolute effect size was very small; the level may be graded up if there is a large or very large effect size or if a significant dose-response relationship is demonstrated.
[b]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

RCT = randomized controlled trial.

time of the writing and editing of this document, 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 Levels of Evidence (Level 1a to 5) (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 the American Academy of Pediatrics (AAP) Steering Committee on Quality Improvement and Management (SCQIM)[10] (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 on 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.

B | 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 two independent reviewers (Figure II.A-2). Each iterative reviewer evaluated the completeness of the identified literature and evaluated whether EBRRs 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 on by the initial author and the 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 on all changes before each section was allowed to proceed into the final ICAR statement stage.

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 (ie, 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).

C | ICAR:O Statement

After the review and completion of all topic sections, the principal editor (Z.M.P.) 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 article was produced.

TABLE II.A.3 AAP-defined strategy for recommendation development

Evidence quality	Preponderance of benefit over harm	Balance of benefit and harm	Preponderance of harm over benefit
A. Well-designed RCTs	Strong recommendation	Option	Strong recommendation against
B. RCTs with minor limitations; overwhelmingly consistent evidence from observational studies	Recommendation		
C. Observational studies (case-control and cohort design)			Recommendation against
D. Expert opinion, case reports, reasoning from first principles	Option	No recommendation	

AAP = American Academy of Pediatrics; RCT = randomized controlled trial.

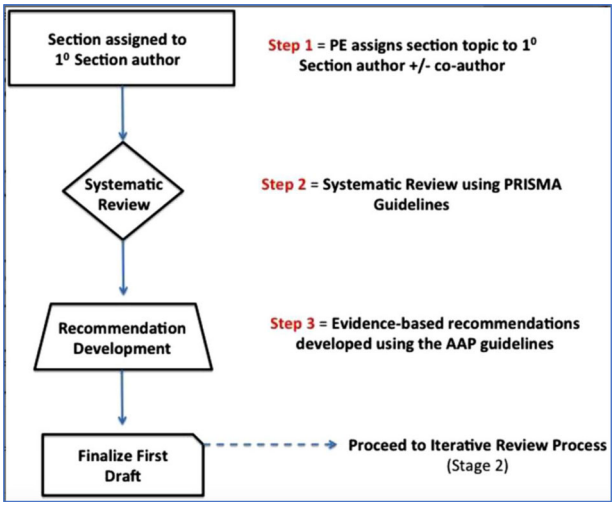

FIGURE II.A-1 Stage I of Iterative Review Process

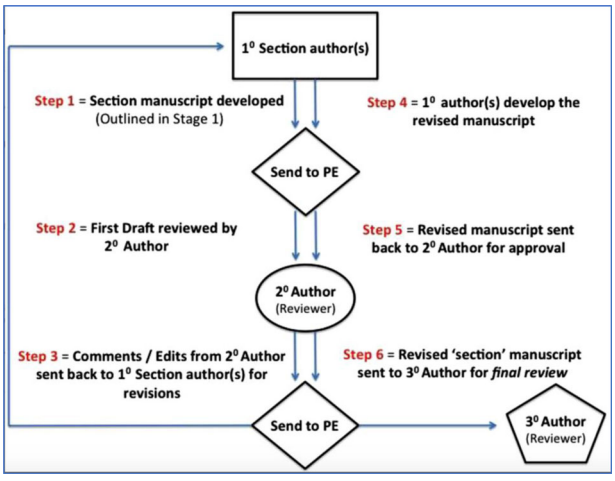

FIGURE II.A-2 Stage II of Iterative Review Process

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.[11–13] While anosmia, by definition, describes complete smell loss, functional anosmia refers to the possible existence of trace olfactory function (OF) but at a level not considered to be useful or noticeable in daily life.[12,14] Hyposmia or microsmia is defined as partial smell loss.[12,14] Specific anosmia is an inability to detect one or more specific odorants while olfaction of other odorants is intact.[15]

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 patients with complete loss of smell.[12,13,16] Normosmia (normal OF) for most olfactory tests is based on normative data from healthy 16- to 35-year-old patients, although normative data have been collected for all age groups on certain tests, such as the University of Pennsylvania Smell Identification Test (UPSIT®).[13] Hyposmia is an absolute score below the 10th percentile of that normosmic group.[12,16,17] Hyposmia can be further delineated into mild, moderate, or severe hyposmia.[13] OF 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.[14]

B | Parosmia

Parosmia is defined as a qualitative dysfunction from a distorted perception of smell in the presence of an odor object.[18] 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."[19–23] 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 simply "strange" to inducing powerful feelings, such as nausea, and preventing normal food intake.

C | Phantosmia

Phantosmia is defined as a qualitative dysfunction of smell in the absence of an odor object.[24] 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."[25–28] It is often difficult for the individual 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.[27,28]

IV | INDIVIDUAL BURDEN OF OD

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.[29] OD hence disturbs functioning of all of those domains. As a consequence, a substantial number of affected individuals state that they experience a poorer overall quality of life (QOL),[30] which particularly affects emotional well-being and interpersonal relationships. Evidence of the costs of smell impairment are summarized below with regard to both aspects (Table IV.1 and Tables IV.2-IV.4).

Emotional state

Previous research has repeatedly demonstrated associations between decreased olfaction and anhedonia or depression.[31–33] Because of largely shared neural pathways (eg, amygdala, hippocampus, insula, and orbitofrontal cortex [OFC]),[34] this link is not surprising. Croy and Hummel[31] suggest that possible mechanisms behind this association might include that: (1) dysfunction of the OB (as the initial station of olfactory processing) results in decreased neural signaling into subsequent cortices; or (2) the consequence of depressive behavior (eg, withdrawal) leads to diminished olfactory input and consecutive diminished OF. Regardless of the mechanisms involved, negative feelings such as anhedonia, sadness, fear, or frustration are reported by about one third of patients with olfactory loss,[30,35,36] with varying prevalence attributable to individual patient characteristics. For example, higher prevalence has been reported in patients with hyposmia versus those with anosmia,[37] while evidence regarding sex effects is mixed,[37,38] but with women reporting particular effects in social domains.[36] 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 with other demographic groups.[39] Individuals with reduced self-esteem have been shown to be prone to the emergence of depressive symptoms from olfactory losses.[40] Single reports disclose disturbances in a wide array of life areas, including hygiene behavior, domestic life,[36] or the enjoyment of simple pleasures, such as the smell of flowers, perfumes, or nature.[41] In view of these reports, the low general QOL 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 are obtained from patients seeking help, thus suggesting selection bias.[30,42] 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.[44] For such predisposed populations, suitable interventions, eg, 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[45] or emotional states,[46–48] personality traits,[49] and the genetic constitution[50] of the releaser. Familiar body odors can signal comfort,[51,52] and may be associated with affectionate

TABLE IV.1 Section evidence summary: Emotional state

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Stevenson[29]	2010	4	Literature review	Animal studies, olfactory loss in patients, human studies on evidence of that function	Identification and categorization of the main functions of human olfaction	Identification of three major classes of functions: ingestion, avoiding environmental hazards, and social communication with specific subfunctions
Croy, Nordin, and Hummel[30]	2014	4	Literature review	Quantitative and qualitative, and patients with congenital olfactory disorder	Links between olfactory impairment and general QOL/depression	Olfactory impairment associated with disturbances in various life areas (food, harmful event detection, social situations); majority of patients with olfactory disorder deal well but a limited proportion experience reduced QOL and increased depression scores
Croy and Hummel[31]	2017	4	Literature review	Healthy individuals, depressed patients, patients with olfactory disorder	Links between olfaction and depression	Interaction between olfaction and depression by two suggested pathways: (1) impaired OF as a consequence of reduced olfactory attention and input; and (2) OD as a marker for enhanced vulnerability to depression
Kohli et al[32]	2016	4	Literature review	Primary depression patients or primary patients with OD	Links between OD and depression	Reciprocal relationship: depressive patients show reduced olfactory performance, patients with OD exhibit depressive symptoms
Schablitzky and Pause[33]	2014	4	Literature review	Healthy individuals, distinct groups of major depressive disorder, bipolar disorder, seasonal affective disorder	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 mood	Major depressive disorder relates to reduced olfactory sensitivity but not to odor identification/discrimination, no associations in bipolar disorder/seasonal affective disorder but in healthy individuals exhibiting subclinical depressive states

(Continues)

TABLE IV.1 (Continued)

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Rochet et al[34]	2018	4	Literature review	Healthy individuals, depressed and clinically improved patients, patients with OD	Links between olfaction and depression, olfactory markers of depression	Olfactory impairment affects QOL/daily life, associations with depression; (heterogenous findings regarding olfactory markers of depression Reciprocal relationship between OD, depression/QOL
Erskine and Philpott[35]	2019	4	Case series, qualitative research	Patients with smell disorder	Subjective experiences of patients with smell disorder	Identified themes: negative emotional impact, feelings of isolation, impaired relationships and daily functioning, impact on physical health, and the difficulty in and financial burden of seeking help
Philpott and Boak[36]	2014	3	Cohort	Patients with OD	Consequences of smell disorder on patients' daily life and affected areas	OD associated with psychological impairment and reduced life quality: 43% of the patients reported depression, 45% anxiety, 92% impairment of eating, 57% isolation, and 54% relationship difficulties; women were more affected then men
Frasnelli and Hummel[37]	2005	2	Cross-sectional controlled	Patients with OD (quantitative and qualitative) and HCs	Qualitative and quantitative OD and impact on daily life	Patients with parosmia as well as quantitative OD show higher rates of daily life complaints when compared with patients experiencing quantitative olfactory impairment only; patients with quantitative olfactory impairment exhibited more complaints than HCs
Desiato et al[38]	2020	1	Systematic review and meta-analysis	Study cohorts recruited from the general population	Prevalence of OD in the healthy general population	Overall prevalence of OD of 22.2%; reported higher prevalences when measured with expanded identification tests <8 items and in patients aged >55 years

(Continues)

TABLE IV.1 (Continued)

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Murr et al[39]	2018	2	Prospective controlled	Patients with OD and HCs	Importance of olfaction	Highest importance of olfaction in young, healthy women (aged ≤25 years); patients with OD reported decreased importance of olfaction; possible coping mechanism
Kollndorfer et al[40]	2017	2	Prospective controlled	Patients with anosmia and HCs	Link between self-esteem and QOL in OD	Decreased life quality and reduced body-related self-esteem in patients with anosmia; low life quality and self-esteem related to depressive symptoms
Keller and Malaspina[41]	2013	4	Patient-report series	Patients with OD	Subjective experiences with olfactory loss	Impaired life quality, in particular reflected by reported social isolation and anhedonia
Blomqvist et al[42]	2004	3	Cohort	Patients with OD	Well-being and coping in patients with olfactory loss	Impaired life quality (eg, physical health, financial security, social relations, leisure, and emotional stability) and negative effects on well-being; patients use problem- and emotion-focused coping
Oleszkiewicz et al[43]	2020	2	Cohort	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 nonaffected individuals in cognitive functioning but not in well-being and chemosensory communication
Schäfer, Schriever, and Croy[44]	2021	4	Literature review	Patients with OD and 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 with concomitant impairment caused by smell loss; provide treatment and coping strategies

LOE = level of evidence; OD = olfactory dysfunction; OF = olfactory function; QOL = quality of life.

TABLE IV.2 Section evidence summary: Interpersonal relationships

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Lobmaier et al[45]	2018	2	Cross-sectional experimental	Healthy individuals, men rating women's 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[46]	2015	2	Cross-sectional experimental	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[47]	2011	2	Cross-sectional experimental	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[48]	2009	2	Cross-sectional experimental	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[49]	2012	2	Cross-sectional experimental	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[50]	1995	2	Cross-sectional experimental	Healthy individuals, women rating men's body odors	Link between major histocompatibility complex, body odor, and attractiveness	More pleasant perception of body odors when major histocompatibility complex dissimilar; preference erased in women taking oral contraception
Rattaz et al[51]	2005	2	Cross-sectional experimental	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

(Continues)

TABLE IV.2 (Continued)

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Granqvist et al[52]	2019	2	Cross-sectional experimental	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 individuals
Lundström and Jones-Gotman[53]	2009	2	Cross-sectional experimental	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[54]	2016	3	Cohort	Healthy individuals, parents	Links between child-rearing and olfaction	Parents actively seek their child's odor in daily rearing; the child's head is the most frequent source of affective experiences and the child's bottom of practical
Croy, Nordin, and Hummel[30]	2014	4	Literature review	Quantitative, qualitative, and congenital OD	Links between olfactory impairment and general QOL/depression	Olfactory impairment associated with disturbances in various life areas (food, harmful event detection, social situations); majority of patients with OD deal well but a limited proportion experience reduced QOL and increased depression scores
Drummond, Douglas, and Olver[55]	2013	4	Case series, qualitative research design	Patients with severe TBI and olfactory loss	Impact of olfactory impairment on daily activities and social participation	OD has a significant impact on various activities and social role
Keller and Malaspina[41]	2013	4	Patient-report series	Patients with OD	Subjective experiences with olfactory loss	Impaired life quality, in particular reflected by reported social isolation and anhedonia
Brämerson, Nordin, and Bende[56]	2007	3	Prospective cohort	Patients with OD	Description of how quantitative and qualitative olfactory disorders are diagnosed, what the causes are, and how QOL is compromised in patients	Patients with reduced sense of smell, often combined with qualitative disorders, exhibit significantly reduced QOL, particularly in paid employment, household work, and social and family life

(Continues)

TABLE IV.2 (Continued)

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Erskine and Philpott[35]	2019	4	Case series, qualitative research design	Patients with smell disorder	Subjective experiences of patients with smell disorder	Identified themes: negative emotional impact, feelings of isolation, impaired relationships and daily functioning, impact on physical health, and the difficulty in and financial burden of seeking help
Lundström et al[57]	2013	2	Cross-sectional	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[58]	2019	2	Cross-sectional	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[59]	2019	4	Literature review	Healthy individuals, patients with OD	Links of olfactory ability and romantic relationships	Body odor perception moderates mate choice and provides a source of comfort in existing relationships, and alteration of preference may signal the breakdown of a relationship
Herz and Inlicht[60]	2002	3	Cohort	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[61]	2018	2	Cross-sectional	Healthy individuals	Body odor attractiveness and human leukocyte antigen similarity	Women not using hormonal contraception rated human leukocyte antigen–similar body odors as less attractive; no influence of human leukocyte antigen similarity was observed for women using hormonal contraception and men

(Continues)

TABLE IV.2 (Continued)

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Bendas, Hummel, and Croy[62]	2018	2	Cross-sectional	Healthy individuals	Link between odor threshold and sexual desire, sexual experience, and sexual performance	High olfactory sensitivity relates to higher pleasantness of sexual activities and higher frequency of orgasms in women
Croy et al[63]	2012	2	Cross-sectional	Congenital anosmic patients and HCs	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[64]	2019	2	Cross-sectional	Patients with smell disorder 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 OF; no differences in standardized questionnaire
Oleszkiewicz et al[43]	2020	2	Cohort	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 nonaffected individuals in cognitive functioning but not in well-being and chemosensory communication

HC = healthy control; OD = olfactory dysfunction; OF =olfactory function; QOL = quality of life; TBI = traumatic brain injury.

feelings.[53,54] OD is thus likely to be associated with deficits in receiving, processing, and interpretation of such interpersonal sensory information. Patients with olfactory disorders frequently complain about impairment in social situations, isolation, or feelings of social insecurity.[30,41,55] This is of significant relevance in the context of intimate relationships, such as relationships between parent and child or between romantic partners.[35,56] Regarding the former, parents report the body odor of their child as an affective and instrumental cue,[54] as infant odor is associated with neural correlates of reward in the maternal brain.[57,58] The latter was studied by Mahmut and Croy[59] who reported evidence for the involvement of olfaction in the "initiation, maintenance, and breakdown of romantic relationships." As body odors signal attractiveness[60,61] or mediate sexual experience[62] in normosmic individuals, dysosmic patients exhibit a reduced number of sexual partners and experience enhanced partnership insecurity,[63] as well as reduced sexual desire, which can affect intimacy and pleasure.[64] 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,[65.66] which, in turn, might be a predictor for depressive symptoms. However, again, this association has only been found for individuals troubled enough by their olfactory impairment to seek professional help, and not by those who are unaware and unaffected by their deficit.[43]

OD can affect interpersonal relationships and emotional state.

Aggregate grade of evidence: B (Level 1: one study; Level 2: 20 studies; Level 3: five studies; Level 4: 12 studies).

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

TABLE IV.3 Section evidence summary: Increased hazard exposure

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Ahmedy et al	2020	3	Case-control	32 adults post-TBI with olfactory loss, and 32 adults post-TBI with no olfactory loss	Survey completion	Decreased QOL, with 71% fearing "exposure to hazardous substances (eg, gas, smoke)," compared with 15% of controls
Altundag et al	2015	3	Cohort	199 of 2824 patients admitted to hospital who indicated OD	Survey completion	Decreased QOL, with 49% almost or always "scared of getting exposed to certain dangers (eg, gas, rotten food)"
Barillo et al	1996	4	Case series	727 fire fatalities in New Jersey, 1985–1991	Fatalities from fire	Children aged <11 years and elderly aged >70 years represented a disproportionate percentage of fire victims
Blomqvist et al	2004	4	Case series	72 patients with anosmia (46%) or hyposmia (54%)	Survey completion	Perceived main risk of failure to detect fire/smoke (42%), rancid food (19%), dangerous chemicals (12%)
Bonfils et al	2008	3	Case-control	57 hyposmics and 49 controls	Reported occurrence of hazardous events	Patients with OD had an increasing likelihood of experiencing all hazardous events
Chalke et al	1957	4	Case-control	61 patients aged >65 years and 30 patients aged <65 years	Ability to smell "odour of town gas"	Approximately 33% of elderly patients were unable to smell gas, compared with 7% of controls
Croy et al	2011	3	Case-control	235 anosmic/hyposmic and 235 normosmic individuals	Individual Importance of Olfaction Questionaire completion	Olfactory-impaired individuals attach less importance to smell in daily life than controls.
Croy et al	2012	3	Case-control	32 patients with idiopathic congenital anosmia, 36 age-matched normosmic HCs	Survey completion	Anosmics were significantly more likely to report household accidents (eating spoiled foods, burning food, burning clothes ironing, problems perceiving smoke, general accidents in household) than controls
Keller et al	2013	4	Case series	1000 with self-reported OD	Survey completion	72% "scared of exposure to dangers"
Miwa et al	2001	3	Retrospective cohort	Smell clinic–tested patients: impaired = 345, improved = 75	Survey completion	The impaired group had higher disability and lower QOL than the improved group

(Continues)

TABLE IV.3 (Continued)

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Nordin et al	2011	4	Case series	50 patients with NPs	Survey completion	38% perceived risk of failure to detect smoke/fire, 15% rancid food, 6% dangers at work, chemicals/gases
Pence et al	2014	3	Retrospective cohort	704 smell clinic–tested patients with varying levels of impairment (643) and without (161)	Reported occurrence of hazardous events	Increasing likelihood of experiencing hazardous event with increasing OD
Santos et al	2004	3	Retrospective cohort	445 smell clinic–tested patients with varying levels of impairment (340) and without (105)	Reported occurrence of hazardous events	Increasing likelihood of experiencing hazardous event with increasing OD
Sorokowska et al	2020	3	Cohort	100 blind and 100 sighted controls, 74 deaf and 99 hearing controls	Threshold for detection of rotten food odor	No differences in odor detection, suggesting no sensory compensation in patients who are vision or hearing impaired
Temmel et al	2020	4	Case series	278 patients with OD	Survey completion	Decreased QOL; 50% ate spoiled foods, 30% burned foods; younger and female patients were more likely to have complaints/issues

HCs= healthy controls; LOE = level of evidence; NP = nasal polyp; OD = olfactory dysfunction; QOL = quality of life; TBI = traumatic brain injury.

humans, while much attention is directed toward the impact of OD on feeding behaviors and QOL,[67–69] 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.[69] Objective data directly linking smell loss to such potential harms are lacking. An early study attempted to explore causes of the disproportionate number of deaths in persons aged >60 years in England caused by "coal-gas poisoning," demonstrating that 33% of those aged >65 years, compared with 7% aged <65 years, were unable to recognize the odor of "town gas."[70] 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 with state demographics, arguing that this might be explained, in part, by reduced olfaction in the latter group.[71] Studies employing patient reports of having experienced OD-related safety events showed significant differences between anosmic, hyposmic, and normosmic populations for both acquired[72–74] and congenital[75] olfactory deficits. The odds ratio of experiencing "hazardous events" compared with controls was 2.94 for anosmics and 1.30 to 2.18 for hyposmics of varying degrees, while increased risk was also noted in patients aged <65 years and women, potentially related to differing risks of exposure during work and home activities.[74] However, difficulties exist in normalizing data for frequency of exposure to such events, as well as length or nature (quantitative versus qualitative) of OD. Many studies have explored the QOL impact of OD. Those including safety-related issues have indicated increased incidence of fear or concern for gas leaks (49%–60%[67,68,76,77]), smoke/fires (30%–50%[68,77–80]), chemical exposures (6%–40%[68,80]), and eating spoiled foods (15%–71%[67,76–80]). However, only two of these studies employed some form of olfactory-intact control population, with one relying on patient-report of function,[68] and the other using objective testing.[67] 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 anosmic compared with hyposmic or control patients,[81] suggesting compensation among afflicted individuals. However, research does not

TABLE IV.4 Section evidence summary: Increased mortality

Study	Year	LOE	Study design	Population	Outcome	Conclusions
Wilson et al[83]	2011	2	Longitudinal cohort	Retired Chicago-area adults, mean age 79.7 years	All-cause mortality; mean 4.2 years	Difficulty with odor identification is associated with increased risk of death
Gopinath et al[84]	2012	2	Longitudinal cohort	Australian adults aged ≥60 years	All-cause mortality; 5 years	The relationship between olfaction and mortality may be largely mediated by cognitive impairment
Pinto et al[85]	2014	2	Longitudinal cohort	US adults aged ≥57 years	All-cause mortality; 5 years	OF is one of the strongest predictors of 5-year mortality in a nationally representative sample of older US adults
Devanand et al[86]	2015	2	Longitudinal cohort	New York City adults, Medicare beneficiaries aged ≥65 years	All-cause mortality; mean 4.1 years	Anosmia is a particularly strong predictor of dementia
Schubert et al[87]	2017	2	Longitudinal cohort	Beaver Dam, WI, adults aged 53–97 years	All-cause mortality; mean 12.8 years	Olfactory impairment, but not hearing or visual impairment, is associated with increased mortality
Ekström et al[88]	2017	2	Longitudinal cohort	Swedish adults aged 40–90 years	All-cause mortality; 10 years	Presence or absence of dementia does not attenuate the association between olfactory loss and mortality
Leschak and Eisenberger[89]	2018	2	Longitudinal cohort	Older US adults aged ≥57 years	All-cause mortality; 5 years	Social network size partially mediated the olfactory-mortality link in women (nationally representative samples of older US adults)
Laudisio et al[90]	2019	2	Longitudinal cohort	Italian adults aged ≥65 years	All-cause mortality; 9 years	The relationship between olfaction and mortality may be mediated through frailty, possibly via inflammation
Liu et al[91]	2019	2	Longitudinal cohort	Pittsburgh, PA, and Memphis, TN, adults aged 70–79 years	All-cause and cause-specific mortality; 3, 5, 10, and 13 years	Neurodegenerative diseases and weight loss explain only part of the increased mortality
Choi et al[92]	2021	2	Cohort study with National Death Index follow-up	US adults aged >40 years	All-cause mortality; 5 years	Objective (but not subjective) OD is associated with increased mortality among older (≥65 years) but not middle-aged (40–64 years) US adults

LOE= level of evidence; OD = olfactory dysfunction; OF = olfactory function.

support cross-modality compensation among sensory-impaired individuals. Thresholds for detection of rotten food odor showed no differences between blind or deaf individuals or unimpaired controls.[82]

Limited primarily subjective data suggest an increased risk of personal safety events, as well as deficits in QOL 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.

OD affects personal safety.

Aggregate grade of evidence: C (Level 4: 14 studies; Level 5: one study).

C | Increased Mortality

Olfaction has been linked to a number of conditions, most notably neurodegenerative disease and the ultimate health outcome: mortality.

The first paper to connect impairment in odor identification (using the Brief Smell Identification Test, or B-SIT) with increased, adjusted risk of death was published by Wilson et al[82] in 2011 in the Rush Memory and Aging Project, a prospective, longitudinal study of the development of Alzheimer disease (AD). Consequently, Gopinath et al[83] examined this question in the Blue Mountains Eye Study in Australia. Although they found a relationship between the San Diego Odor Identification Test (SDOIT) score and increased risk of all-cause mortality, the association was not significant after adjustment for cognition. Pinto et al[84] demonstrated a robust relationship between poor odor identification (5-item Sniffin' Sticks [SS] test) and odds of mortality in the National Social Life, Health, and Aging Project (NSHAP), a nationally representative data set. Using the 40-item UPSIT®, Devanand et al[85] showed increased hazard of death for patients in the lower quartiles of function compared with those in the highest quartile in a multiethnic community cohort from New York City, using the Washington Heights/Inwood Columbia Aging Project. Schubert et al[86] examined data from EHLS (Epidemiology of Hearing Loss Study), a population-based longitudinal study of sensory function and aging in Beaver Dam, WI, and found that sensory dysfunction predicted mortality but was specific to olfaction (8-item SDOIT) and not hearing or vision. Ekström[87] 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 [SOIT]) was not mediated by conversion to dementia before death, suggesting that the mechanism was not solely via the development of neurodegenerative disease. Similarly, examining underlying mechanisms, Leschak et al[88] 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[89] found that OD (self-reported inability to detect at least two of three common odors) was associated with reduced survival, an association that varied according to frailty and systemic inflammation (serum increased interleukin [IL] 6 levels) in a prospective population-based study of the development of late-life disability in Tuscany, Italy, (InChianti [Invecchiare in Chianti] study). Recently, Liu et al[90] found a close connection between decreased odor identification (B-SIT) and death in the Health, Aging, and Body Composition study, which examined older adults from Pittsburgh, PA, and Memphis, TN. 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[91] linked 2013–2014 National Health and Nutrition Examination Survey (NHANES) participants to the National Death Index and found that objective olfactory impairment predicted 5-year mortality in patients aged ≥65 years but not in middle-aged patients after 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 assessed odor identification. We note that they do so in completely different ways using different forms of testing, both long and short. All studies controlled for key confounding factors and all include objective measures. The analysis strategy varies among the studies (eg, logistic regression, cox analyses, and hazard ratios). Nevertheless, almost all of these studies found robust (excepting the Blue Mountains Eye study) and consistent relationships between poor olfaction and subsequent mortality (time to follow-up ranged from 4.1 to 13 years). Several provide dose- response analyses. Thus, the aggregate LOE 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.

Decrease in olfaction is associated with increased mortality.

Aggregate grade of evidence: B (Level 2: 10 studies).

V | ANATOMY AND PHYSIOLOGY

A | Olfactory Epithelium to Olfactory Bulb

The peripheral olfactory organ is the OE, a true neuroepithelium that lines the olfactory cleft (OC) 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.[92–95] 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 glands. Deep to the OE lies a lamina propria containing olfactory nerve fascicles with nonmyelinating ensheathing glia, blood vessels, and Bowman 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 PBs, terminating on specific glomeruli.[96] Odor molecules reaching the OC are detected by olfactory receptors (ORs), G-protein–coupled receptors expressed on neuronal immotile cilia embedded in the mucus layer at the OE surface.[97,98] Odorant molecules use the mucus layer to bind to these receptors, and binding triggers OSN depolarization. The OR family in humans contains ≈350 genes, and evidence suggests that a given OSN generally expresses a single OR.[98,99] Distinct ORs are activated by specific sets of odors and may be broadly or narrowly tuned.[100] Each OB glomerulus receives input from a subset of OSNs expressing the same OR proteins.[101] In this way, the pattern of glomerular activation in the OB 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.[102–104] 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.[105,106] In animal models, OE basal cells can produce OSNs, sustentacular cells, and microvillar cells.[107,108] Olfactory injury and repair has been well studied in rodent models,[109–111] and evidence suggests that similar repair mechanisms are active in adult humans.[99] Nonetheless, acquired olfactory disorders in humans and the potential recovery from them—or lack thereof—remain incompletely understood.

B | Olfactory Bulb to olfactory cortical structures

The axonal projections from the sensory neurons of the OE are conveyed by the olfactory nerve (cranial nerve I) to the 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 regions 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.[113] 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.[114] 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.[113] 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 OFC both directly and via the mediodorsal nucleus of the thalamus.[113]

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.[115] 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.[116] In contrast, the projection of the bulb onto the piriform cortex is spatially diffuse[114]; the axons of M/T cells receiving synaptic input from a single glomerulus disperse among

the piriform cortex, and the projections from functionally disparate glomeruli are largely indistinguishable from each other.[117] 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.[117] In terms of odorant representation in the piriform cortex, spiking activity is sparse and likewise distributed.[118,119] 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.[120] At the higher cortical level, the OFC also seems to integrate odorant and reward information to help guide motivated behavior.[121]

VI | INCIDENCE AND PREVALENCE

The absolute precise incidence and prevalence of olfactory disorders are still unknown. Despite increasing efforts to characterize and diagnose OD and its numerous causes, prevalence rates range widely from ≈1.5% to 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 OD increases in prevalence with age and is more common in men relative to women.[122,123]

The methods of olfactory assessment used in epidemiologic studies vary widely. Although a multitude of dedicated olfactory assessment tools are available worldwide, self-reported OD is a commonly used metric.[123,124] While self-report measures are valuable, these assessments typically lack sensitivity and underestimate the degree of OD as compared with psychophysical instruments.[125,126] Nonetheless, the lack of an accepted, universal psychophysical instrument, coupled with wide variation in patient demographics, exposures, and cultural differences among studies, makes determination of prevalence rates challenging.[122]

Self-reported prevalence rates have been explored in several large, population-based studies. A survey of ≈80,000 US adults aged >18 years, utilizing national adjustment estimates, extrapolated that 1.4% of the US adult population experienced olfactory impairment. This prevalence rate markedly increased in older individuals, with 40% of individuals aged >65 years reporting OD.[127] Meanwhile, olfactory questionnaires from a nationally representative Korean database reported a prevalence rate of OD of 4.5%.[128] Two additional studies in Europe and the United States, using questionnaires aimed primarily at determining the prevalence of CRS, reported prevalence rates of OD of 7.6% and 9.4%, respectively.[129,130]

Between 2011 and 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 whether they experienced a smell disturbance in the preceding 12 months; however, when considering participants with self-reported changes in OF "since age 25," prevalence rates increased to ≈23%.[131,132] Meanwhile, psychophysical assessment using the Pocket Smell Test (PST) demonstrated rates of 12.4% and 13.5% from the 2011 to 2012 and 2013 to 2014 interview cycles, respectively.[133,134] In the same database, 6.5% of participants experienced phantom odor perception.[135]

Several additional large population-based studies have included psychophysical measures of OF. Utilizing the SOIT in a nationally representative population from Sweden, the prevalence of OD was 19.1%, with nearly 6% of participants designated as anosmic.[136] Notably, self-reports of "worse-than-normal" olfaction was 15.3% in the same population.[137] An Australian investigation of participants from in and around Sydney, using the SDOIT, identified impaired olfaction in 27% of participants.[138] 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.[139]

Multiple US-based studies have utilized both self-reporting and psychophysical testing. In a large cohort of participants from Wisconsin, OD was identified in 24.5% of all participants and 62.5% of participants aged >80 years, as defined by the SDOIT.[125] Additional US-based studies examining aged populations with various psychometric olfactory instruments have reported rates of OD from 2.7% to 100%, with significant variation regarding the definitions of dysfunction, study size, participant demographics and age.[140–146]

Overall, OD is a common condition, with a wide range of prevalence among 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 men.

VII | PATHOPHYSIOLOGY

A | Sinonasal Inflammatory Disease

1 | Basic underlying mechanisms

Sinonasal inflammatory disease is the most common cause of olfactory loss.[146–148] Olfaction relies on conduction of odorants from the air to the OE and subsequent sensorineural signaling to the brain. Clinical and basic science

TABLE VII.1 Section evidence summary: Basic underlying mechanisms of sinonasal disease related olfactory loss

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Youngentob et al[153]	1986	4	Case series	10 HCs	• Perceived odorant intensity • Perceived sniffing effort	Olfactory magnitude decreases with increased nasal resistance
Seiden et al[150]	2001	3	Prospective cross-sectional	All-comers with change in smell/taste perception (n = 420)	• UPSIT®	Etiology of olfactory loss may help guide prognosis and response to steroids
Lane et al[165]	1996	3	Prospective case series	Pollen-sensitive patients (n = 8)	• Nasal patency • UPSIT®	Alterations in nasal patency do not correlate with OF
Klimek et al[166]	1997	2	Prospective case-control	Grass allergy (n = 17), HC (n = 12)	• NVF • ECP • CCCRC olfactory test	Decrease in olfaction during allergy season correlated to ECP but not NVF
Lee et al[189]	2000	5	In vitro	18 explants from 6 normosmic patients, 45 explants from 15 anosmic patients	• Map5 • Cellular morphology • T&T olfactometer	Significantly decreased number of OR cells and abnormal morphology in anosmic specimens
Kern[190]	2000	5	In vitro	120 OE explants (26 patients with CRS, 4 HCs)	• UPSIT® • Histologic inflammatory changes	OE has a similar inflammatory infiltrate in CRS as respiratory epithelium; inflammatory changes may contribute to olfactory deficit
Stevens[159]	2001	4	Prospective case series	24 patients with CRSwNP with anosmia	• UPSIT®	Surgery resolved anosmia in 12 of 24 patients; oral but not intranasal steroid sprays improved anosmia in 9 of the 12 remaining patients
Hornung et al[154]	1997	4	Case series	12 HCs	• Custom odors	Use of nasal dilators increases odorant identification and intensity and decreases threshold
Landis et al[152]	2003	2	Prospective case-control	HCs (n = 56) vs patients with CRSwNP (n = 42)	• SS-ID (10 odors) • Odorized powder identification	Retronasal OF is retained over orthonasal in the presence of NPs in the anterior portion of the OC
Pfaar et al[151]	2006	1	RCT	HCs with sponges in OC (n = 20) or respiratory epithelium (n = 13)	• SS-ID • Odorized powder identification	Orthonasal but not retronasal odor indentification is significantly decreased after obstruction of the OC

(Continues)

TABLE VII.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Zhao et al[155]	2006	4	Case report	1 patient with CRSwNP	• CFD olfactory airflow • Odorant delivery rate • Psychophysical olfactory assessment	Surgical remodeling of the nasal airway is a significant factor in recovering OF
Yee et al[191]	2010	3	Prospective, case-control	Patients with CRS (n = 50), HCs (n = 20)	• PEA threshold test • Histological analysis of neuronal, nonneuronal, and inflammatory cells • Univerity of Miami staging system	Patients with CRS demonstrated metaplasia and lower percentages of normal epithelium and OSNs; patients with CRS patients anosmia most likely to have OE erosion, highest density of eosinophils, and most extensive abnormalities on CT
Hox et al[167]	2010	3	Prospective study	Patients with CRSwNP (n = 65)	• VAS • SNOT-22 • SF-36 • PNIF • SS-ID • Eosinophilia	Olfaction correlates to blood eosinophilia but not PNIF or VAS for obstruction
Selvaraj et al[164]	2012	3	Prospective crossover	11 HCs	• SS test	Nasal irrigation with an ion concentration that mimics mucus composition in chronic inflammation induces a significant elevation of olfactory thresholds
Mori et al[158]	2013	3	Prospective cross-sectional	228 patients with CRS, and 190 patients with ECRS	• T&T olfactometer • Intravenous olfactory test • Likert scale • Ethmoid opacification • OC polyps	OD was more severe in patients with ECRS; ethmoid opacification and OC polyps were associated with OD in patients with CRS
Henkin et al[196]	2013	3	Retrospective case-control	59 patients with hyposmia, 6 HCs	• 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[199]	2014	1	Meta-analysis	4 RCTs of subjective olfaction after oral steroids in patients with CRSwNP (n = 236) 2 RCTs of objective olfaction after oral steroids in patients with CRSwNP (n = 147)	• SF-36 • PST®® • BAST-24	Oral steroids significantly improve subjective and objective measures of olfaction in patients with CRSwNP

(Continues)

TABLE VII.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Alobid et al[163]	2014	2	RCT	Moderate to severe CRSwNP, steroid treatment (n = 67), controls (n = 22)	• BAST-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[162]	2014	3	Prospective cross-sectional	Patients with CRS 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[195]	2016	3	Prospective cross-sectional	CRSwNP (n = 15) CRSsNP (n = 19)	• SS-TDI • Cytokine bead assay	IL-5 levels were inversely correlated with all patients with CRS, whereas IL-6, IL-7, and VEGF levels were positively correlated only in patients with CRSwNP
Hauser et al[193]	2017	3	Prospective case-control	CRSwNP (n = 32) CRSsNP (n = 27) HCs (n-10)	• UPSIT® • Lund-Mackay • SNOT-22 • Tissue eosinophilia	Tissue eosinophilia is associated with olfactory loss in patients with CRSwNP independent of disease severity
Lavin et al[192]	2017	3	Prospective, case-control	CRSwNP (n = 36) CRSsNP (n = 37) HCs (n = 26)	• UPSIT® • OC opacification • CLC protein • ECP	Markers of eosinophils are elevated in the superior turbinate of patients with CRS and correlate with olfactory loss
Wu et al[194]	2018	3	Prospective, case-control	CRSwNP (n = 36) CRSsNP (n = 31) HCs (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, and IL-13 are correlated with reduced olfactory scores
Nishijima et al[156]	2018	4	Case series	CRSwNP (n = 21) HCs (n = 4)	• CFD olfactory airflow • Odorant uptake • T&T olfactometer	Olfactory airflow and olfaction are differentially affected by NP location
Victores et al[203]	2018	5	In vitro	CRS (n = 11) HCs (n = 9)	• Expression of phosphorylated c-Jun	Explants from patients with CRS demonstrated increased phosphorylated c-Jun in olfactory neurons with an associated loss of neurons

(Continues)

TABLE VII.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Valsamidis et al[161]	2019	3	Prospective case-control	60 patients with septal deviation 25 HCs	• SS-TDI • NOSE • QOD	Septoplasty leads to improvement in smell perception and improved QOL
Chen et al[184]	2019	5	In vitro	32 patients with 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[197]	2019	3	Prospective cross-sectional	CRSwNP (n = 61) CRSwNP (n = 49)	• UPSIT® • Lund-Mackay • Inflammatory cell counts • OC cytokine bead assay	Hierarchical cluster analysis revealed that OD 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[157]	2020	2	Prospective case-control	CRSsNP (n = 73) CRSwNP (n = 75) HCs (n = 30)	• SS-TDI • Lund-Mackay	OD correlates with OC opacification and Lund-Mackay score in patients with CRSwNP but not those with CRSsNP
Soler et al[198]	2020	3	Prospective cross-sectional	CRSwNP (n = 37) CRSsNP (n = 25)	• SS-TDI • Lund-Mackay • OC opacification • OC cytokine bead assay	Th2-related inflammatory proteins are more often found in OC mucus of patients with CRSwNP and correlate with OD and opacification on CT

AERD = aspirin-related respiratory disease; BAST-24 = Barcelona Smell Test-24; CCCRC = Connecticut Chemosensory Clinical Research Center; CCL = chemokine (C-C motif) ligand; CFD, computational fluid dynamics; CLC = Charcot-Leyden crystal; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; CRSsNP = chronic rhinosinusitis without nasal polyps; CT = computed tomography; ECP = eosinophil cationic protein; ECRS = eosinophilic chronic rhinosinusitis; HC = healthy control; IL = interleukin; LOE = level of evidence; Map5 = microtubule-associated protein 5; NOSE = Nasal Obstruction Symptom Evaluation; NP = nasal polyp; NVF = nasal volume flow; OC = olfactory cleft; OD = olfactory dysfunction; OE = olfactory epithelium; OF = olfactory function; OR = olfactory receptor; OSN = olfactory sensory neuron; PEA = phenylethyl alcohol; PNIF = peak nasal inspiratory flow; PST = Pocket Smell Test; QOD = Questionnaire of Olfactory Disorders; QOL = quality of life; RCT = randomized controlled trial; RSDI, Rhinosinusitis Disability Index; SF-36 = 36-Item Short Form Health Survey; SNOT-22 = 22-item Sino-Nasal Outcome Test; SS = Sniffin' Sticks; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale; VEGF = vascular endothelial growth factor.

research suggests that disruption of both of these mechanisms contributes to 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 OC.[149,150] Increased resistance to airflow has been associated with decreased perception of odor strength[151] that improves with nasal valve dilation.[152] Computational fluid dynamics in patients with

CRS with nasal polyps (CRSwNP) has shown variation in airflow disruption based on polyp location that correlates to the degree of OD, with the greatest dysfunction in patients with OC polyps and the least dysfunction with polyps confined to the middle meatus.[153,154] Similarly, OC opacification on computed tomography (CT), reflective of OC patency, has been shown to correlate with OD differentially by CRS type.[155,156] Removal of obstruction either through surgical[157–159] or anti-inflammatory[160,161] treatment results in similar levels of improvement in olfaction. Additionally, chronic inflammation has been speculated to alter olfactory mucus composition, impeding conduction of odorants.[162]

While airflow patency plays an important role, it does not fully correlate with the degree of olfactory loss in sinonasal inflammatory disease,[163–165] suggesting the contribution of other mechanisms. In contrast to conductive loss, sensorineural OD involves disruption of OSN signaling and processing. The pseudostratified OE is composed 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.[166–168] Horizontal basal cells provide a secondary, quiescent stem cell pool that is activated after severe injury.[169,170] The signaling pathways that guide regeneration are incompletely understood, but include p63 and Notch[171–173] in mice, and appear to be modulated by inflammatory mediators such as tumor necrosis factor (TNF)[174–180] and nuclear factor-κB–mediated cross-talk between horizontal basal cells and immune cells.[181,182] 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,[182–186] with similar findings noted in specimens from anosmic patients.[187–190] Markers of inflammation, such as tissue eosinophilia[190,191] and the presence of type 2 cytokines in mucus obtained from the OC,[164,192–196] have been reported to correlate with olfactory loss in patients with CRSwNP.

The OE is impacted by, and likely participates in, sinonasal inflammatory disease, with varying contributions of conductive and sensorineural mechanisms on OF and OE structure. Medical therapy that targets inflammation likely improves olfaction both by increasing airflow and by reducing local inflammatory cells and mediators.[148,157,161,197] The expression of steroid receptors on OE cells [198,199] in animal models and the attenuation of OE lesions after topical administration of steroids may suggest additional direct effects of corticosteroids on OE function.[200] 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.[201,202]

Sinonasal inflammatory disease as a cause of olfactory dysfunction.

Aggregate grade of evidence: B (Level 1: one study; Level 2: one study; Level 3: nine studies; Level 4: one study).

Decreased odorant conduction as a mechanism of inflammation-associated OD.

Aggregate grade of evidence: B (Level 1: one study; Level 2: three studies; Level 3: three studies; Level 4: five studies).

Sensorineural mechanisms as an underlying cause of inflammation-associated OD.

Aggregate grade of evidence: C (Level 3: three studies; Level 5: four studies).

2 | Related to CRS

a. In relation to phenotype (nasal polyps or no nasal polyps)

The degree of OD commonly varies by CRS phenotype, with patients with CRSwNP usually demonstrating a higher prevalence and severity of olfactory impairment than patients with CRSsNP.[203–208] The factors contributing to olfactory loss in patients with CRS are complex and likely a consequence of multiple pathophysiological mechanisms that may differ depending on phenotype. Mechanical obstruction of odorant transmission to the OC neuroepithelium can be a result of mucus, edema, and/or nasal polyps (NPs) and is usually more severe in patients with CRSwNP.[209,210] As noted in the prior section, in this mechanism, the polyps and edema characteristic of the CRSwNP phenotype block odorants from reaching the OC. Among patients with CRSwNP, OC opacification on CT scan correlates with the severity of OD.[211] Differences in orthonasal versus retronasal OF have been demonstrated, with retronasal OF better preserved compared with orthonasal function among patients with CRSwNP.[211,212] Patients with CRSsNP tend to have less OC opacification on CT scan, suggesting less disruption of odorant delivery as compared with CRSwNP.[211] Direct inflammation at the level of the neuroepithelium is another possible mechanism of CRS-related olfactory loss.[213] In this mechanism,

TABLE VII.2 Section evidence summary: CRS related olfactory loss in relation to phenotype

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Wu[225]	2018	3b	Case-control	CRS (n = 67) CRSwNP (53.7%) CRSsNP (46.3%) HCs (n = 12)	Olfactory testing immediately before surgery (UPSIT®) Olfactory mucus protein analysis	OF and inflammatory mediators were largely dependent on polyp status Mucus protein levels (cytokines [IL-2, IL-5, IL-6, IL-10, and IL-13]) inversely correlated with OF by identification testing among the overall cohort IL-2, IL-5, IL-6, and IL-10 showed a negative correlation with OF among patients with CRSsNP; however, this was not statistically significant IL-5 and IL-13 were independent predictors of OF among all patients Elevated levels of IL-5 and IL-13 were seen among patients with CRSwNP compared with patients with CRSsNP
Kern[226]	2009	3b	Case-control	CRS (n = 26) HCs (n = 4)	Biopsy olfactory mucosa for histopathologic analysis Preoperative olfactory testing (UPSIT®)	19 biopsy specimens had olfactory mucosa 9 patients had normal olfactory mucosa and normal OF (UPSIT® >35) 10 patients had pathologic changes in olfactory mucosa, with 7 of these patients having olfactory deficits 3 patients had normal OF despite moderate chronic inflammation
Soler[227]	2020	4	Cross-sectional	CRS (n = 62) CRSwNP (59.7%) CRSsNP (40.3%)	Olfactory testing (SS-TDI) 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[228]	2017	3b	Case-control	CRS (n = 59) CRSwNP (54.2%) CRSsNP (45.8%) HCs (n = 10)	Olfactory testing immediately before surgery (UPSIT®) 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 per high-power field, $P < 0.05$) and lower age-/sex-adjusted UPSIT® scores (−17.4 vs −6.2, $P<0.001$) when compared with CRSsNP

(Continues)

TABLE VII.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
						UPSIT® scores were strongly negatively correlated with tissue eosinophil counts in patients with CRSwNP ($r = -0.60$, $P = 0.0003$) but not patients with CRSsNP ($r = 0.16$, $P = 0.42$)
Ganjaei[229]	2018	4	Case series	CRS (n = 70) CRSwNP (58.5%) CRSsNP (41.4%)	Olfactory testing: retronasal and orthonasal (SS-TDI)	Higher prevalence of anosmia was seen among patients with CRSwNP vs patients with 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 patients with CRSwNP vs patients with CRSsNP Retronasal identification was worse among patients with CRSwNP vs patients with CRSsNP
Othieno[230]	2018	4	Case series	CRS (n = 69) CRSwNP (58.0%) CRSsNP (42.0%)	Olfactory testing: retronasal and orthonasal (SS-TDI) OC endoscopy score	Strong correlation between retronasal and total orthonasal olfaction scores were seen among all patients ($r = 0.77$, $P < 0.001$) Retronasal olfaction scores were worse among patients with 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[231]	2017	4	Cross-sectional	CRS (n = 73) CRSwNP (49.3%) CRSsNP (50.7%) HCs (n = 26)	Olfactory testing (SS-T and UPSIT®) obtained in a subset of patients Tissue biopsies Gene expression of CLC protein CT and endoscopic analysis	Superior turbinate tissue of patients with CRSwNP had significantly increased eosinophilic inflammation, and olfactory threshold deficits were significantly associated with NP status, as well as superior turbinate eosinophilia, even after controlling for NP status
Soler[215]	2009	4	Cross-sectional	CRS (n = 147) CRSwNP (44.9%) CRSsNP (55.1%)	Smell identification testing (UPSIT®) Mucosal histopathologic findings (ethmoid cavity)	Higher mucosal eosinophil counts correlated with worse UPSIT® scores ($r = -0.253$; $P = 0.002$)

(Continues)

TABLE VII.2 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
						Mucosal eosinophils (>5 per high-power field) present in 66.7% of patients with CRSwNP Lower SIT in eosinophilic CRSwNP compared with noneosinophilic CRSwNP (19.3 ± 11.3 vs 25.1 ± 9.8; $P < 0.001$) No correlation between mucosal eosinophil counts and UPSIT® scores among patients with CRSsNP
Gudziol[224]	2009	4	Case series	CRSwNP (n = 19) HCs (n = 18)	Preoperative and 3-month postoperative olfactory testing (SS-TDI) and MRI volumetric measurement of OB	Increase in OBV 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 OBV nor olfactory testing was seen among control group
Rombaux[223]	2008	4	Case series	CRSsNP (n = 22) HC (n = 16)	Olfactory testing: retronasal and orthonasal (SS-TDI) MRI volumetric measurement of OB Lund-Mackay score	No difference in OBV among patients with CRSsNP vs controls OBV was inversely correlated with Lund-Mackay score ($r = -0.52$, $P = 0.001$), scores ≤12 had larger OBVs compared with scores >12) Higher Lund-Mackay score correlated with worse retronasal OF (r=–0.040, P=0.014) but not with orthonasal OF
Landis[214]	2003	4	Case series	CRSwNP (n = 42) HCs (n = 56)	Olfactory testing: retronasal and orthonasal SS-ID (10 odors)	Better retronasal than orthonasal OF in the presence of anterior OC obstruction with CRSwNP No difference between retronasal and orthonasal smelling among controls

CLC = Charcot-Leyden crystal; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; CRSsNP = chronic rhinosinusitis without nasal polyps; CT = computed tomography; HC = healthy control; IL = interleukin; LOE = level of evidence; MRI = magnetic resonance imaging; NP = nasal polyp; OB = olfactory bulb; OBV: olfactory bulb volume; OC = olfactory cleft; OF = olfactory function; SIT = Smell Identification Test; SS-ID = Sniffin' Sticks identification only; SS-T = Sniffin' Sticks threshold only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

odorants may reach the OC but inflammatory changes of the neuroepithelium disrupt transduction. In CRSsNP animal models where inflammatory mediators such as TNF-α were directly induced in olfactory inflammation, neuronal cell death and inhibition of OE proliferation were observed.[209,210] This neuroepithelial inflammation was temporary and resulted in reversible interference in odorant transduction. In patients with CRSwNP, mucosal inflammation and tissue eosinophilia (>5 eosinophils per high-power field) have been associated with worse objective OF at baseline.[213] Following sinus surgery, improvements have been reported among patients with nasal polyposis and eosinophilia.[214–216] In the section to follow on endotyping, studies have also found a correlation between olfaction and the level of inflammatory proteins found in OC mucus, including IL-5, IL-13, and

IgE, among others. Although these inflammatory proteins are most commonly seen in patients with CRSwNP, they may also be elevated in patients with CRSsNP, suggesting that phentoypes are not always reflective of underlying endotype.[213] OC neuroepithelium remodeling represents another potential mechanism for CRS olfactory loss.[217] Biopsy of the OC in patients with chronic inflammation has shown changes to the neuroepithelium, with resulting squamous metaplasia, fibrosis, or replacement of the OE with respiratory epithelium.[218–220] Several studies have also found associations between olfaction and OB remodeling.[220,221] When examining objective disease burden among patients with CRSsNP, higher severity of sinonasal inflammation has been associated with smaller OB volumes (OBVs) and decreased retronasal OF.[221] Inflammatory-related changes in the olfactory neuroepithelium, as previously described, are postulated to result in decreased sensory input to the OB resulting in a decrease in OBV. Additionally, among patients with CRSwNP, changes in OBVs have been examined in response to medical and surgical treatment with a correlation observed between improvement in OF and increase in OBV.[222]

b. In relation to endotype

CRS has been traditionally classified based on clinically observed phenotype,[230] eg, the presence (CRSwNP) or absence (CRSsNP) of NPs, the presence of aspirin-sensitivity (aspirin-related respiratory disease [AERD]), or the presence of fungal elements in allergic fungal sinusitis.[231–234] The CRSwNP and AERD phenotypes have significantly higher prevalence of OD, 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 such as CRSwNP may have significant endotypic heterogeneity in different parts of the world.[235–237] 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 OF 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 OC 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,[238–241] 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.[242] 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 OC appear consistently related with OD as measured using both the UPSIT® and SS 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 OD in more than one independent study.[240,241]

While these studies do elucidate inflammatory mediators present in the OC among patients with OD, 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, with the identified inflammatory factors also correlated with edema in the narrow OC, as measured by radiographic opacification.[241] Interestingly, in the studies that have separated analyses out by CRSsNP and CRSwNP phenotypes, the associations between endotype and OF appear significant primarily among patients with CRSwNP, suggesting that the effects of type 2 inflammation explain a greater portion of the variance in OF among these patients.[241] Currently, there are no studies that 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 of sinus surgery.[243]

The two biologic medications specifically targeting aspects of type 2 inflammation in CRSwNP included objectively measured olfaction as an end point.[244–246] 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.[247,19] Omalizumab, in contrast, targets soluble and cell-bound IgE. Evidence that both of these precision biological medications improved olfactory outcomes in patients with CRSwNP relative to placebo provides evidence that these

TABLE VII.3 Section evidence summary: CRS related olfactory loss in relation to endotypic factors

Study	Year	LOE	Study design	Study groups	Sample studied and olfactory testing method	Endotypic factors associated with olfactory findings
Schlosser[240]	2016	2	Cross-sectional	34 patients: 19 with CRSsNP and with 15 CRSwNP	OC mucus SS-TDI	IL-5 was associated with worse overall SS-TDI score and identification
Lavin[241]	2017	2	Cross-sectional	30 patients: 7 controls, 10 with CRSsNP, and 13 with CRSwNP	Superior turbinate tissue UPSIT® and SS-T before ESS	CLC protein gene expression was associated with worse UPSIT® and threshold scores
Wu[242]	2018	2	Cross-sectional	67 patients: 31 CRSsNP, 36 CRSwNP	OC mucus UPSIT® before ESS	IL-2, IL-5, IL-6, IL-10 and IL-13 were significantly associated with SIT scores
Morse[244]	2019	2	Cross-sectional	110 patients: 49 with CRSsNP and 61 with CRSwNP	Middle meatal mucus UPSIT® before ESS	A cluster characterized by high IL-5 and IL-13 levels had significantly higher objective olfactory deficit; however, IL-5 and IL-13 alone were not independently associated when AERD status and CT score were modeled
Wu[245]	2020	2	Longitudinal after sinus surgery	76 patients: 36 with CRSsNP and 30 with CRSwNP	Superior turbinate mucosa SS-TDI	Preoperative eosinophilia was associated with objective olfactory decline
Soler[243]	2020	2	Cross-sectional	62 patients: 25 with CRSsNP and 37 with CRSwNP	OC mucus SS-TDI	IL-5, IL-6, IL-13, IL-9, IL-10, IL-23, CCL2, CCL3, and IgE were associated with TDI score Correlations between inflammatory mediators and olfaction only were observed among patients with CRSwNP

AERD = aspirin-related respiratory disease; CCL = chemokine (C-C motif) ligand; CLC = Charcot-Leyden crystal; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; CRSsNP = chronic rhinosinusitis without nasal polyps; ESS = endoscopic sinus surgery; CT = computed tomography; IL = interleukin; LOE = level of evidence; OC = olfactory cleft; SIT = Smell Identification Test; SS-T = Sniffin'Sticks threshold only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification; TDI = threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

inflammatory effects directly or indirectly cause olfactory deficit and provide the impetus for endotyping-based approaches to study CRS-associated olfactory loss.

CRS endotyping is associated with OF.
Aggregate grade of evidence: C (Level 4: five studies).

3 | Related to AR or CRS

Extensive evidence supports the association between rhinosinusitis and 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 ≈30% of patients with non-AR, 13% with AR, and 12% of healthy individuals.[248] In South Korea, a diagnosis of OD was strongly associated with AR compared with healthy individuals (odds ratio, 4.88).[249] In a systematic review of 36 studies, OD was observed in 10% to 90% of patients with AR, with most studies reporting between 20% to 40%.[250] This finding is corroborated among pediatric populations; one study identified a significant increase in OD only for pediatric patients whose symptoms exceeded 3 years.[251–254] One explanation for the wide range of OD in this population is that some studies have included patients with comorbid CRS.

A variety of subjective and objective metrics have been used to assess OF in patients with rhinitis. The severity of OD is typically within the mild to moderate range; true anosmia is rare.[250,255,256] Patients with perennial AR or non-AR 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.[251,257,258] Suzuki et al[259] demonstrated that patients with seasonal AR for ≥10 years, in particular, experience extra-seasonal OD.

Fewer studies have specifically investigated the effects of non-AR on olfaction. Some evidence suggests higher rates and more severe OD in patients with non-AR compared with patients with AR, but this finding is inconsistent among the published literature.[248,254,260,261]

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 OC.[262] However, the literature more strongly supports the notion that inflammatory cytokines detrimentally affect the function of the olfactory mucosa.[251,258,261–263] Murine models of AR have demonstrated OD secondary to infiltration of eosinophils, mast cells, plasma cells, macrophages, and neutrophils in the OE.[264–266] A study by Kim et al[265] demonstrated that mice with AR exhibited higher rates of olfactory stem cell apoptosis induced by TNF-α with a synergistic effect from IL-5.

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

OD is associated with rhinitis.

Aggregate grade of evidence: C (Level 2: seven studies; Level 3: three studies; Level 4: nine studies).

B | Postviral 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 postviral OD (PVOD) for years before the pandemic. The pathophysiology of PVOD following an infectious illness has not been clearly delineated.[267] 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 OD 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.[267–270] One recent study has shown rhinovirus and coronavirus to be the most commonly identified viruses in PVOD.[271] Viruses have been shown to damage a variety of cells within the olfactory system including OR neurons, which detect odorants and odorant-binding proteins.[268] Other studies have shown that the olfactory neuroepithelium undergoes cellular changes caused by viral insult.[267] These changes include the replacement of the neuroepithelium with respiratory-like epithelium, a highly disorganized OE compared with patients without OD, and occasionally metaplastic squamous epithelium.[272,273] Other studies show that there is an increase in neurogenesis in response to the viral insult.[274] This results in a larger proportion of immature neurons compared with mature neurons, which may impact overall olfactory ability. Additionally, dendrites in the epithelium of patients with postinfectious olfactory disorders have been shown to be truncated and not able to reach the surface layer as would be seen in healthy tissue.[272–274] 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.[275,276] 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 with others. These studies suggest that viral infections drive OD in varying ways depending on 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 causes.

In addition to the previously mentioned viral effects on OE in relation to PVOD, there is also the acute onset of nasal congestion that hinders OF and often accompanies a viral infection.[277] Nasal congestion limits the airflow among the OE, and without proper airflow, odorants are unable to be detected by the OE. This process is acute and short-lived, and the sense of smell would theoretically return once the inflammation subsides. Unfortunately for some patients, OD persists, likely because of neuroepithelial injury after this acute stage. The exact percentage of patients with persistent OD is not well-defined because the total incidence of postviral olfactory loss (PVOL) is not known, although this group makes up ≈20% to 30% of most series accounting for the etiology of OD in patients presenting for treatment.[278] Nonetheless, 35% to 46% of patients with PVOD will gain clinically

TABLE VII.4 Section evidence summary: AR or non-AR related olfactory loss

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Olsson et al	2003	2	Cross-sectional	10,670 adults	Self-reported questionnaire	In a population study, 19% of individuals reported symptoms consistent with non-AR, while 24% reported AR. Subjective hyposmia was reported by ≈30% in non-AR, 13% in AR, and 12% in healthy individuals
Rhee et al	2014	2	Cross-sectional	2305 participants	IgE testing Health survey	Prevalence of AR was 16% Odds ratio of OD for those with AR of 4.88 compared with a healthy population
Stuck and Hummel	2015	2*	Systematic review	36 studies N =17 to 10,670 patients	Effect of AR on olfaction	OD in AR ranges from 20% to 40%, typically mild to moderate
Aksoy et al	2018	3	Case-control	44 pediatric patients with seasonal AR	CCCRC olfactory test Subjective olfactory assessment Acoustic rhinometry Allergy prick testing	CCCRC olfactory test scores significantly decreased during allergy season, which correlated with subjectively reported hyposmia Nasal volume decreased during allergy season but there was no correlation between CCCRC olfactory test score and acoustic rhinometry
Mariño-Sanchez et al	2018	4	Cross-sectional	142 pediatric patients with persistent AR	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	1260 pediatric patients with AR (CRS not excluded)	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	Control group: 45 pediatric patients AR: 42 pediatric patients Non-AR: 35 pediatric patients	SS-TDI	No significant difference in odor scores was found between groups or based on severity; however, odor identification and total odor scores were lower in patients with symptoms for >3 years
Katoto-michelakis et al	2015	3	Cross-sectional	Control group: 48 healthy patients Placebo-control group: 45 patients with AR Treatment group: 145 patients with AR	SS-TDI Questionnaire of Olfactory Deficits QOL surveys	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 HCs

(Continues)

TABLE VII.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Klimek et al	2017	4	Case series	47 patients with persistent AR	SS-TDI	Mean baseline TDI score of the cohort was 23.7 (±3.9), consistent with hyposmia (≤30.5).
Moll et al	1998	4	Case-control	28 patients with seasonal AR 47 patients with perennial AR Control group: 66 healthy patients	CCCRC olfactory test	When tested intraseasonally, both patients with perennial and seasonal AR exhibited OD as compared with controls Extraseasonally, only odor threshold testing was significantly lower in patients with seasonal AR as compared with controls
Klimek and Eggers	1997	4	Case-control	17 patients with AR (grass pollen) Control group: 12 healthy patients	CCCRC olfactory test NVF Eosinophilic cation protein levels	Odor discrimination and identification similar in AR and control patients preseasonally, but odor thresholds decreased in the AR group Intraseasonal testing revealed OD in the AR group, which correlated with nasal eosinophilic cation protein levels
Suzuki et al	2018	4	Case-control	50 control patients 50 patients with AR for <10 years 50 patients with AR for ≥10 years	Odor identification (Open Essence test) Odor detection Odor threshold	OD existed in >50% of patients with AR for ≥10 years OD exists extraseasonally in patients with AR for ≥10 years
La Mantia et al	2018	4	Case-control	AR: 50 patients Non-AR: 40 patients Mixed rhinitis: 32 patients	SS-TDI	Patients with non-AR exhibited a significantly lower TDI score consistent with greater OD as compared with patients with AR or mixed rhinitis
Guss et al	2009	4	Case-control	31 patients with AR 10 patients with AR + CRS 10 patients with non-AR	UPSIT® CT sinus Allergy Prick Testing	50% of patients with AR exhibited hyposmia. No significant difference between patients with CRS in addition to AR. Patients with non-AR had a lower UPSIT® score ($P = 0.06$).
Sivam et al	2010	2	RCT	Placebo control group: 9 patients with AR Mometasone treatment group: 8 patients with AR	Nasal symptoms UPSIT® Histopathology examination of OE	Of 17 patients with AR, 12 exhibited mild to moderate OD at baseline, 2 were anosmic, and 3 had normal OF

(Continues)

TABLE VII.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Becker et al	2012	4	Case-control	Seasonal AR: 23 patients Perennial AR: 16 patients Control group: 33 patients	SS-TDI Nasal secretion analysis 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, with no correlation with TDI score
Jung and Hyo Kim	2020	2	RCT	Control group: 8 mice Local nasal allergy: 8 mice Systemic allergy: 8 mice Positive controls: 8 mice Budesonide treatment group: 8 mice	Odor detection Histopathologic evaluation 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 examination
Kim et al	2019	2	RCT	Control group: 25 mice AR: 25 mice	Immunohistochemical staining	Mice with AR exhibited reduced numbers of olfactory sphere cells (neural stem cells) with increased apoptosis TNF-α and IL-5 synergistically induce stem cell apoptosis
Ozaki et al	2010	2	RCT	Control group: 10 mice AR group: 10 mice	1 Odor detection 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

AR = allergic rhinitis; CCCRC = Connecticut Chemosensory Clinical Research Center; CRS chronic rhinosinusitis; HC = healthy control; IL = interleukin; NVF = nasal volume flow; OD = olfactory dysfunction; OE = olfactory epithelium; QOL = quality of life; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, identification; TNF-α, tumor necrosis factor α; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

*Level of evidence (LOE) downgraded because of heterogeneity of results and lack of randomized controlled trials (RCTs).

significant improvement.[279] For those who do not recover, the pathophysiology of OD may be the result of several underlying factors.

Postinfectious changes can extend further along the olfactory pathways. PVOD decreases the size of the OB on imaging studies.[280] The volume of the OB negatively correlates with the level of OD.[281] It is unclear whether the OB is decreasing in size because of the lack of neural input caused by damage in the OE or whether the OB is decreasing as a direct impact from viral damage in the bulb itself.[282] Viral inoculation in the nostrils of mice have shown spongiotic damage to the OB likely related to the infiltration of the bulb by lymphocytes and neutrophils. The OBs in the inoculated mice were still decreased 5 months after injection.[274] Another study also showed direct cellular damage at the level of the OB in mice when inoculated with the influenza virus.[283] 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.[284] Another study found IL-6 to be sig-

TABLE VII.5 Section evidence summary: non–COVID-19 Post Viral Olfactory Dysfunction

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Rombaux et al	2009	4	Retrospective cohort	122 patients undergoing psychosocial and electrophysiologic recordings after chemosensory stimuli 50 patients undergoing imaging for OB measurements	SS-TDI Electrophysiologic responses MRI measurements of OB	Hyposmia was more prevalent than anosmia 35 patients showed olfactory ERPs 109 patients had trigeminal ERPs Greater decrease in OB size correlated with greater loss of smell
Kattar et al	2020	1	Systematic review	NA	NA	OT demonstrates clinically significant improvement in PVOD
Cavazzana et al	2018	3	Retrospective cohort	791 patients underwent SS test at first and final visits	SS-TDI	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	NA	NA	PVOD is complex with many possible mechanisms
Suzuki et al	2007	4	Cross-sectional	24 patients with PVOD	Identification of virus present in a patient with OD	Rhinovirus in 10 patients, coronavirus in 1 patient, parainfluenza in 1 patient, and Epstein-Barr virus in 3 patients
Wang et al	2009	4	Case-control	25 patients with PVOD 22 controls	Identification of PIV3	22 of 25 patients had positive PIV3 epithelial samples compared with 2 of 22 positive PIV3 epithelial samples
Tian et al	2021	4	Cross-sectional	151 patients with PVOD were enrolled, with samples taken from 38 patients who visited within 3 months of symptom onset	SS-TDI Detection of viruses in OC specimens	Rhinovirus detected in 13 of 38 patients Coronavirus OC43 detected in 1 of 38 patients
Jafek et al	2002	4	Cross-sectional	Unknown number of patient samples	Histopathologic slides of nasal epithelium biopsies	Replacement of the neuroepithelium with respiratory-like epithelium, a highly disorganized OE, and metaplastic squamous epithelium

(Continues)

TABLE VII.5 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Mueller et al	2005	4	Case-control	22 patients had post-URI olfactory deficits 9 patients had posttraumatic olfactory deficit 17 HCs	SS-TDI MRI using CISS sequence	Presence of smell dysfunction is associated with reduced OBVs
Yao et al	2018	4	Case-control	19 controls 19 cases	Volumetric measurements of the OB	Decrease in size of the OB 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 OD	SS-TDI MRI of OB	10 patients were normosmic Those who were hyposmic/anosmic on SS test had a higher detection rate of OB atrophy
Henkin et al	2013	3	Case-control	59 patients (26 men and 33 women) who had varying degrees of smell loss 9 controls (5 men and 4 women)	OF measured by detection thresholds and recognition thresholds Plasma, urine, parotid saliva, and nasal mucus samples	Plasma levels of IL-6 were significantly elevated in patients with OD compared with controls

CISS = constructive interference in steady state; ERP = event-related potential; HC = healthy control; IL = interleukin; LOE = level of evidence; MRI = magnetic resonance imaging; NA = not available; OB = olfactory bulb; OC = olfactory cleft; OD = olfactory dysfunction; OBV = olfactory bulb volume; OE = olfactory epithelium; OF = olfactory function; OT = olfactory training; PIV3 = parainfluenza virus 3; PVOD = postviral olfactory dysfunction; SS = Sniffin' Sticks; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; URI = upper respiratory infection.

nificantly elevated in the plasma, saliva, and nasal mucosa of patients with hyposmia. IL-6 is a known proinflammatory cytokine that is present in other chronic diseases.[285] 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 performed to identify the exact underlying mechanisms of chronic OD following viral infections, and whether this is consistent or varies depending on the infecting virus. The complexity of olfaction allows for many possible pathways. Nonetheless, current data suggest that the changes to the neuroepithelium and OB may be the key areas in the pathophysiology of postinfectious OD (PIOD).

OD can occur after viral infection.

Aggregate grade of evidence: C (Level 2b: two studies; Level 3c: two studies; Level 4c: eight studies).

2 | COVID-19 related

Otolaryngologists were the first to draw attention to COVID-19–related smell loss and champion its role as an early, and often only, sign of COVID-19 infection.[286–288] Despite the rapidly growing evidence base, the exact mechanisms underpinning the pathophysiologic basis for OD 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 coexist: conductive loss caused by OC obstruction, injury to the OE, and injury to the OB.

Conductive anosmia

Impairment of nasal airflow caused by nasal obstruction will restrict delivery of odorants to the OE, a

common cause of short-term olfactory impairment associated with the "common cold" caused by endemic coronaviruses.[289,290] 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 (URIs),[292] suggesting that an alternative or additional mechanism may be responsible.

Nevertheless, localized obstruction caused by edema within the OC has been proposed as one potential mechanism, and one study has shown a high prevalence of complete obstruction of the OC in MRI scans performed within 15 days of onset of COVID-19 OD,[292] which had resolved in more than half of cases at 1-month follow-up, accompanied by improvement in OF. In contrast, other radiological studies of patients with more persistent loss have found this to be an uncommon persistent finding.[293] 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 OE

Olfactory epithelial injury has been demonstrated in prior cases of postviral loss and could account for the transient edema noted in the OC discussed above. Histological studies in prior non–COVID-19 cases of postviral loss have demonstrated damage to the OE including OSNs and consequent scarring and atrophy, with correlation found between the severity of epithelial destruction and OD.[294] A postmortem study of two patients with COVID-19 reporting anosmia showed focal atrophy of the OE, leukocytic infiltration of the lamina propria, and evidence of axonal damage in the olfactory nerve fibers.[295] Similarly, animal models of SARS-CoV-2[11] have demonstrated massive destruction of the OE after nasal inoculation and loss of cilia, with evidence of recovery observed as early as day 4 after exposure, although 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 OE, but not on the OSNs themselves.[297,298] Staining from a preclinical study showed that SARS-CoV-2 infected the sustentacular cells but not OSNs, and the virus was not found in the OB or central nervous system (CNS).[299] The sustentacular cells support olfactory receptor neuron function in a number of ways, including endocytosing odorant-binding proteins, removing toxic volatiles, and supplying glucose to the cilia of the olfactory receptor neuron. Therefore, damage to these cells may precipitate reduced sensitivity and the loss of cilia from the OSNs, resulting in OD 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 to 14 days,[300–302] faster than would be expected for immediate OSN replacement and maturation but in keeping with the faster recovery of sustentacular cells.[303] 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 consistent with the presentation of many of these patients with initial recovery from their COVID-19–related loss who then present 3 to 4 months later with a secondary hyposmia, often accompanied by parosmia.

In addition, the immune response may play 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.[297] Persistence of inflammation may prevent recovery of the OE and restoration of the OSNs. Induction of inflammation in a murine model of CRS-associated anosmia demonstrated inhibition of basal cell differentiation and neuronal depletion.[304] Results of olfactory epithelial biopsies from 3 deceased COVID-19 patients showed significantly higher levels of the proinflammatory cytokine TNF-α than biopsies taken from noninfected living controls,[305] although postmortem artifact cannot be excluded. Some of the most recent studies, currently only available 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[306] and olfactory epithelial biopsies harvested from patients with COVID-19 postmortem.[307]

Clinical studies have found that the severity of OD is inversely correlated with recovery rates,[300,301] and may also reflect the severity of epithelial injury. Results of an in vivo biopsy of a patient with anosmia persisting 3 months after diagnosis showed extensive destruction of the OE consistent with mucosal biopsies harvested early in the course of infection in animal models.[308]

OB infection and propagation to the CNS

Propagation of viruses by retrograde axonal transport to the OB and beyond to the CNS is well described[309] and has been shown to be associated with anosmia in herpetic encephalitis[310] in murine models. Animal models of OC43 coronavirus infection have demonstrated viral particles within the OB 3 days after inoculation[311] 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.[312]

A series of 37 MRI scans performed in hospitalized patients with COVID-19 reported signal abnormalities of the OB in 19% of cases.[313] Several case reports documented hyperintensity in the OB, which resolved on repeat imaging 1 month later with subsequent loss of OBV[314–316]; however, it was unclear whether this reflected transient initial edema or subsequent atrophy. Patients with PVOL have previously been found to have reduced volume in the OB and olfactory cortex.[317] One patient with persistent COVID-19–induced OD had MRI performed before COVID-19 infection, which provided baseline volumes of her OB and confirmed significant atrophy of the OB in images performed 2 months after onset.[318] Positron emission tomography imaging found hypometabolism in the gyrus rectus in two patients with persistent COVID-19 OD.[319] 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 OE, and they do not provide direct proof of retrograde transport of SARS-CoV-2 into the OB.

One of the first postmortem 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.[320] A larger postmortem series in preprint demonstrated that three of 32 OB samples were positive for SARS-CoV-2 RNA.[321] In contrast, a series of four postmortem studies failed to demonstrate injury to either the OE or OB, although it was not reported whether these patients reported olfactory deficits.[322]

We are slowly gaining better understanding of how SARS-CoV-2 gains entry into the OSNs and the OB in the absence of ACE2 expression. SARS-CoV-2 may utilize basigin (CD147) and neuropilin-1 as docking receptors on intracerebral vascular endothelial cells in order to cross the blood-brain barrier, while a range of proteases including TMPRSS11A/B, cathepsin B and L, and furin have been shown to facilitate viral cell entry and replication.[323] Alternatively, the virus may gain entry through cerebrospinal fluid (CSF)–filled spaces in perineural nerve sheaths and then into the ventricular system.[324]

Anosmia as a protective mechanism?

The destruction of the OE 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.[325,326] Although this may simply reflect recall bias in patients with more severe symptoms,[327] 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.[328] It has been hypothesized that the damage to the olfactory pathway may be protective in preventing viral entry to the CNS.[329] There is some support from animal models for this theory; destruction of the OE before inoculation has been shown to protect against intracranial invasion in murine studies.[309] Similarly, ablation of the OB can prevent CNS infection after nasal inoculation with a neurotropic coronavirus.[330]

It is possible that post-COVID OD 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 downregulation 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.

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 ORs); (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 post traumatic olfactory loss. In a US national study of 1281 adults, OF was found to be impaired in patients aged ≥40 years in 10.1% who reported loss of consciousness caused by head injury (n = 178) and 10.0% of those reporting serious injury to the face or skull (n = 203).[330] In a study of 114 children with head injuries, olfactory impairment was present in 12% of the cases.[331] Multiple studies have examined the overall occurrence of olfactory impairment following head injury, with reports ranging between 7% and 22%.[330,332–336]

Trauma to the nasal passages and conductive pathways can block airflow and impair OF. Biopsy findings of patients with trauma-related anosmia have revealed injury to the OR cells and cilia.[337] Fractures including frontoorbital and Le Fort fractures have been associated with posttraumatic smell loss. In a study of 5000 patients with injuries to the head or face,[338] 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.[339] Back and forth movement of the brain (coup-contrecoup 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 OBs.[340,341]

Cortical injuries resulting from head trauma, including contusions and bleeding, may result in anosmia, hyposmia, parosmia, or phantosmia. The type of smell loss depends on the brain regions involved.[342] Yousem et al[343] 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 OB and olfactory tracts, subfrontal lobes, and temporal lobes. In a study of 176 combat-blast injuries, 35% of patients with olfactory loss had abnormal findings on brain imaging.[344] Skull base fractures are likely to injure the olfactory nerves and result in complete anosmia.[333] Blows to the back of the head are more likely to result in olfactory loss than blows to the front.[338,345,346] Sports injuries also play a role in olfactory loss. In a study comparing American football players and controls, 17% of the football players had olfactory losses attributed to either a single traumatic brain injury or multiple traumatic brain injuries.[347] Olfactory loss increases with severity of injury, defined by posttraumatic amnesia,[346] Glasgow Coma Scale (GCS), or mild, moderate or severe head injury.[334,348,349] Children with mild head trauma were found to have lower OF scores than an age matched control group.[350] Lower GCS scores in children also correlate with poor performance on olfactory tests.[351]

OD can be caused by head trauma.

Aggregate grade of evidence: C (Level 3: one study; Level 4: 10 studies).

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 OD.[352] There is high likelihood that occupational exposure is underdiagnosed for patients presenting with idiopathic smell disorders.[352] Agents that have been associated with OD include metals (cadmium, manganese, chromium, arsenic, lead, mercury, aluminum, and nickel), organic compounds (butyl acetate, benzene, and benzyl acetate), industrial agents (paint solvents, styrene, and toluene), dusts (cement and hardwood), and nonmetal inorganic compounds (methylbromide, hydrogen sulfide, and chlorine).[353]

Metal exposure occurs in the form of metal dust or vapors.[354] Of the metals, cadmium is the most commonly known to cause olfactory impairment, as this metal targets the first olfactory neuron.[353,355] Cadmium is used in the production of storage batteries and can be present in the environment through waste incineration, sewage, and fertilizers.[356] Previous studies have found a higher prevalence of smell loss and higher olfactory thresholds in cadmium-exposed workers compared with controls, which is directly related with the years of exposure.[355,357–362,363]

Exposure to manganese, another metal, is also associated with OD.[364–368] Inhaled manganese is absorbed by the olfactory neurons and transported from the OB to the olfactory cortex.[369] In manganese-exposed ferroalloy plant workers, high urinary manganese was associated with worsened odor detection thresholds.[368] However, in professional welders exposed to manganese, workers with the highest manganese blood levels exhibited better OF than those with the lowest levels.[359] Whether this effect is transitory before decompensation of the OF is unknown.[366]

Styrene is a solvent used in the plastic industry that has been associated with atrophy of the OE in mice.[370] However, in humans, a study of chronically exposed workers to styrene showed no differences in the phenylethyl alcohol detection threshold and odor identification compared with controls.[371] 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 that 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.[372–377] In a cross-sectional study, respondents with exposure to vapors such as paints, cleaning products, glues, solvents, acids, and welding/soldering fumes were more likely to have experienced olfactory disturbance in the previous 12 months.[366] In past studies, workers in plastic manufacturing had decreased olfactory threshold scores but not in odor identification scores.[378] In a cross-sectional study of Korean workers in automobile repair, printing, shoemaking, and plating industries, all had a higher prevalence of OD compared with office workers.[379]

TABLE VII.6 Section evidence summary: Related to head trauma

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Hoffman et al[334]	2016	4	Cross-sectional national health survey	Responders reporting head injury with LOC (n = 178) Responders reporting serious injury to the face and/or skull (n = 203)	Subjective smell loss + PST	In responders aged ≥40 years, 10.1% of those with head injury and LOC had smell loss and 10.0% of those with facial or skull base injury had smell loss
Schreiver et al[335]	2020	4	Case series	Pediatric patients seen in a smell and taste clinic (n = 164)	SS-TDI	Head trauma was the etiology of smell loss in 12% of patients with OD
Costanzo et al[336]	1986	4	Case series	Patients with head trauma	Not specified	Olfactory impairment occured in 23.6% and 26.6% of motor vehicle accidents and domestic falls, respectively
Ogawa et al[337]	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[338]	2018	4	Case series	Patients with TBI (n = 774)	OF assessed via sensitivity to coffee granules	19.7% of patients with TBI had olfactory impairment This was associated with increased severity of TBI and comorbid medical illnesses
Sumner[339]	1964	4	Case series	Patients presenting with a wide variety of head injuries, from minor to more severe (n = 1167)	Subjective smell loss	7.5% of all head injury patients experienced olfactory impairment 39% experienced some recovery
Temmel et al[340]	2002	4	Case series	Patients with anosmia or hyposmia (n = 278)	SS-TDI	17% of patient with olfactory loss had trauma as a etiology

(Continues)

TABLE VII.6 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Zusho[342]	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 and 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[348]	2015	3	Cohort	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 patients with normal or mild TBI 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[351]	2019	4	Case-control	American football players (n = 75) and HCs (n = 30)	TraQ (Trauma Questionnaire) includes subjective smell questions	17% of American football players had olfactory impairment related to one or multiple TBIs
Schriever et al[354]	2014	4	Case-control	Pediatric patients with mild head trauma (n = 114) and HCs (n = 56)	Modified SS-ID test	Pediatric patients with mild TBI had significantly worsened TDI scores compared with controls but still fell within the normal range

HC = healthy control; LOE = level of evidence; MRI = magnetic resonance imaging; OF = olfactory function; PST = Pocket Smell Test; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TBI = traumatic brain injury; UPSIT® = University of Pennsylvania Smell Identification Test.

TABLE VII.7a Section evidence summary: Related to environmental or work-related toxins

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Adams et al[361]	1961	4	Case-control	106 alkaline battery workers exposed to cadmium and nickel dust 84 controls	Subjective assessment of sense of smell (good, diminished, none) Phenol smell testing	Workers had 15% anosmia, compared with 0% in controls Workers performed more poorly on phenol testing (27.3% vs 4.8%) Anosmia was caused by exposure to cadmium, nickel, or a mixture of both
Potts et al[362]	1965	4	Cross-sectional	70 alkaline battery workers	Percentage of anosmia	65% of anosmia was associated with 10 to 19 years of exposure, 53% with 20 to 29 years of exposure, and 91% with 30 to 40 years of exposure
Ishinini et al[387]	1977	4	Descriptive	Retired workers of arsenic mine		9 of 21 roasters who often worked in the kitchen had dermatitis, depigmentation, septum perforation, hyposmia, anosmia, or peripheral nerve disturbance
Ahlstrom et al[376]	1986	4	Cross-sectional	20 tank cleaners exposed to petroleum Controls (office workers and watchmen)	ODT and perceived odor intensity of 4 stimuli	Tank cleaners had higher absolute odor threshold and normal perception of strong stimuli but impaired perception of weak stimuli
Sandmark et al[377]	1989	4	Cross-sectional	54 painters exposed to organic solvents 42 unexposed controls	UPSIT®	Painters had lower scores, but, in multiple regression analysis, the influence of exposure was not statistically significant The exposure was low, thus an effect for high exposure cannot be ruled out

(Continues)

TABLE VII.7a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Schwartz et al[381]	1990	4	Cross-sectional	187 workers in paint manufacturing	UPSIT®	Dose-related decrements in OF only in nonsmokers
Hotz et al[379]	1992	4	Cross-sectional	264 workers exposed to hydrocarbons Controls	Memory index Subjective smell/taste impairment	8.8% workers with disturbance of smell and taste vs 1.3% of controls
Rose et al[367]	1992	4	Cross-sectional	55 workers with chronic exposure to cadmium fumes in a brazing operation 2 Controls	Urinary cadmium levels Cadmium-induced renal damage OF through butanol detection threshold and odor identification	Of workers, 40% were mildly hyposmic and 13% were moderately or severely hyposmic Of the reference group, 31% were mildly hyposmic Patients with renal damage had more significant OD
Mergler et al[380]	1992	4	Cohort	5 healthy patients exposed to toluene and or xylene	Olfactory perception threshold	6-fold increase of threshold that returned to normal at a rate of 6.8 ds/hour
Wieslander et al[378]	1994	4	Cross-sectional	255 painters (solvent-based paint) 302 exposed to water-based paint	Self-administered questionnaire to assess occurrence of symptoms	Taste or olfactory disturbances were found in 3% of workers exposed to solvent-based paint vs 0.4% in workers exposed to water-based paint
Mergler et al[371]	1994	4	Case-control	115 workers employed in manganese alloy production Matched controls	Emotional state Motor functions Cognitive flexibility Olfactory thresholds for PM-carbinol and toluene Basic mathematics Reading capability Attentional capacity	Manganese workers had significantly worsened smell thresholds compared with their matched controls Pairs differed on emotional state, motor function, cognitive flexibility, and olfactory perception No difference was found in verbal fluency, mathematics, reading, and attentional capacity

(Continues)

TABLE VII.7a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Lucchini et al[372]	1997	4	Cross-sectional	35 male workers of a ferroalloy production plant exposed to manganese oxides Control group of nonexposed workers	Psychomotor function scores Olfactory threshold 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 an effect on the immunological system
Rydzewski et al[365]	1998	4	Cross-sectional	73 workers exposed to cadmium in quantities exceeding maximum allowable concentration	Olfactometry was performed according to Elsberg and Levy's blast-injection method, modified by Pruszewicz	Prevalence of hyposmia of 26.0%, parosmia of 17.8%, and anosmia of 1.4% Correlation between olfaction impairment and cadmium concentration in blood, urine, and workplace air
Sulkowski et al[364]	2000	4	Case-control	73 workers of cadmium-nickel batteries plant 43 controls	Blast-injection threshold measurements (maximum and minimum)	OD in 45.2% of exposed workers and 4.6% of controls Correlation was found between blood/urine cadmium and OD
Schwartz et al[388]	2000	4	Longitudinal	535 former lead manufacturing workers 118 controls	Neurocognitive tests UPSIT®	Significant decline in UPSIT® score in former lead workers
Dalton et al[375]	2003	4	Cross-sectional	Workers exposed to styrene in plastic industry Controls	Threshold for PEA Odor identification Retronasal odor perception	No difference in OF Exposed workers had an elevated styrene ODT (induced adaptation)

(Continues)

TABLE VII.7a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Mascagni et al[359]	2003	4	Cross-sectional	33 workers in cadmium fusion Reference group 1: 39 nonexposed workers Reference group 2: 23 workers exposed to iron and steel welding fumes	PEA odor threshold and confusion matrix odor identification ability Blood and urinary cadmium values	Mean olfactory threshold was significantly worse in cadmium workers Odor identification test findings for cadmium workers were similar to those of the reference groups
Cheng et al[382]	2004	4	Cohort	52 workers exposed to acrylonitrile-butadiene-styrene thermal decomposition products Non exposed reference group (n = 72)	1-butanol threshold Odor identification, both prework and postwork	Exposed group had lower OF after work Exposed workers had decreased olfactory threshold scores but no difference in odor identification scores
Hudson et al[389]	2006	4	Cross-sectional	82 Mexico City residents (high air pollution) 86 Tlaxcala residents (low air pollution)	Olfactory identification and threshold using an orange drink and coffee Odor discrimination using a horchata and atole beverage	Mexico City residents performed worse except those in the 50- to 63-year age group, in which there was no difference
Antunes et al[363]	2007	4	Case-control	Professional welders (n = 43) who worked 1 or 2 years on the San Francisco/Oakland Bay bridge Matched controls	UPSIT® 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[390]	2009	4	Cross-sectional	30 Mexico City residents (high air pollution) 30 Tlaxcala residents	SS-TDI	Mexico City residents performed worse in threshold and discrimination but not in identification
Ranft et al[391]	2009	4	Cross-sectional	399 women exposed to traffic-related particulate matter	SS-ID	Motor vehicle exposure was associated with poorer olfaction

(Continues)

TABLE VII.7a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Calderón-Garcidueñas et al[386]	2010	4	Case-control	OB of: 35 residents of Mexico City exposed to severe air pollution 9 controls UPSIT® scores of: 62 residents of Mexico City 25 controls	UPSIT® Light and electron microscopy of the OB	Mexico City residents had worse UPSIT® scores and OB pathology findings including endothelial hyperplasia and neuronal accumulation of particles
Lucchini et al[368]	2012	4	Cross-sectional	154 adolescents aged 11 to 14 years residing in Valcamonica, Italy (a region impacted by ferroalloy plant emissions containing manganese and other metals for a century), or a reference area Controls in a reference area (n = 157)	Motor coordination (Luria-Nebraska test) Hand dexterity (Aiming Pursuit test) Odor identification (SS-ID) Tremor intensity	Exposure to manganese was associated with deficits in olfactory and motor function
Sorowska el al[392]	2013	4	Cross-sectional	151 native Amazonians 286 residents living in Dresden (higher air pollution)	SS-T	Dresden residents performed worse
Grashow et al[393]	2015	4	Cross-sectional	165 men from the Normative Aging Study who previously had bone lead measurements	UPSIT® score Global cognition (Mini-Mental Status Examination) 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[385]	2016	4	Cross-sectional	Respondents from the NSHAP	Validated odor identification test	Increase in nitric dioxide exposure was associated with increased odds of OD
Riccó et al[394]	2016	4	Cross-sectional	66 workers exposed to phenolic resins	Self-reported olfactory impairment (hyposmia, anosmia, hyperosmia)	31.8% had hyposmia, 18.2% had anosmia, and 13.6% had hyperosmia

(Continues)

TABLE VII.7a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
						High exposure to phenol was the main risk factor for anosmia Exposure to phenol may be associated with self-reported olfactory impairment
Noel et al[370]	2017	4	Cross-sectional, population based	3594 respondents from the 2011–2012 NHANES and 3708 respondents from the 2013–2014 NHANES	Frequency of self-reported smell disorders PST	Exposure to vapors, urinary levels of manganese, 2-thioxothiazolidine-4-carboxylic acid, 2-aminothiazo-line-4-carboxylic acid, 2,4 dichlorophenol, and serum lead levels were all implicated in smell disturbance
Lee et al[383]	2018	4	Cross-sectional	Exposed workers (n = 296) in the automobile repair, printing, shoemaking, and plating industries Nonexposed office workers (n = 99)	OF was evaluated using the Korean SS-ID (8 odors)	In comparison with office workers, the prevalence of OD was higher in the four occupational groups

LOE = level of evidence; NHANES = National Health and Nutrition Examination Survey; NSHAP = National Social Life, Health, and Aging Project; OB = olfactory bulb; OD = olfactory dysfunction; ODT = odor detection threshold; OF = olfactory function; PEA = phenylethyl alcohol; SS-ID = Sniffin' Sticks identification only; SS-T = Sniffin' Sticks threshold only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

Ambient air pollution may also impact OF by contacting the OE, translocating to the OB and migrating to the olfactory cortex causing direct damage of the tissue or inducing local inflammation.[380] In older US adults, exposure to nitrogen dioxide was associated with OD.[381] Residents of cities exposed to severe air pollution have OD demonstrated by worse smell scores than those living in nonpolluted regions. Moreover, the OB showed endothelial hyperplasia and neuronal accumulation of particles.[382]

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

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

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

E | Related to medications

Numerous medications from a broad range of therapeutic classes have been associated with changes in OF. Despite the commonality of medication-related changes in olfaction, there is a paucity of research on both the implicated medications and underlying pathophysiology of OD. The lack of such data are both caused by 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 has many risk factors for baseline OD including advanced age, medical comorbidities, and polypharmacy.[391,392] 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 number of indiscriminate drug interactions.[393]

TABLE VII.7b Section evidence summary: Related to medications

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Walter et al[399]	2014	2	Randomized, placebo-controlled, crossover	Healthy patients (n = 15) Placebo 20-mg oral tetrahydrocannabinol	SS-TDI orthonasal testing at baseline and 2 hours after tetrahydrocannabinol administration	Tetrahydrocannabinol was associated with increased threshold and reduced discrimination scores
Gudziol et al[401]	2006	2	Double-blind, placebo-controlled, crossover	Healthy patients (n = 20) following oral administration of 50 mg of sildenafil, 100 mg of sildenafil, or placebo	SS-TDI and component scores	Reduced discrimination and increased threshold following administration of 100 mg of sildenafil compared with other groups
Jung et al[408]	2011	2	Double-blind RCT	Healthy patients (n = 72) Placebo Phenylephrine Lidocaine Both agents	Korean version of SS-TDI at baseline and 15 minutes postadministration	No difference in TDI scores among groups
Lötsch et al[400]	2001	3	Randomized placebo-controlled	Healthy patients (n = 13) with plasma concentrations of remifentanil (0, 1.2, 1.8, 2.4, 3, 3.6, 4.8, and 6 ng/mL)	SS-TDI at baseline and immediately after infusion completion	Increased threshold scores only with increasing doses of remifentanil
Steinbach et al[402]	2009	3	Prospective cohort study	Chemotherapy for breast or gynecologic malignancy (n = 87)	SS-TDI before, during, directly after, and 3 months following chemotherapy	Chemotherapy has a transient effect on OF TDI was significantly impaired during therapy with near-complete recovery at 3 months Older patients were more affected than younger patients
Alexander et al[414]	2006	4	Retrospective case series	Anosmia after intranasal zinc usage (n = 17)	n-Butanol threshold Identification testing with 7 common odorants and 1 odorant to test trigeminal function UPSIT® (for 9 patients) Clinical history	Impaired threshold and identification in all patients Intranasal zinc–induced anosmia syndrome can be distinguished from postviral anosmia based on history
Davidson et al[415]	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[409]	2018	4	Prospective case series	Healthy patients (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

(Continues)

TABLE VII.7b (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Welge-Lüssen et al[407]	2004	4	Prospective case series	Healthy patients (n = 20) given 1% tetracaine at 3 different locations and then 4% lidocaine in the OC	Self-assessment SS-TDI Olfactory ERPs	1% tetracaine was capable of inducing transient hyposmia but only 4% lidocaine applied directly to the OC could cause transient anosmia
Jafek et al[413]	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[403]	2018	4	Case report, literature review	Propofol as sole anesthetic 6 case reports, dysosmia with varying anesthetics	Clinical history Negative CT/MRI findings	Propofol (and other anesthetics) may cause dysosmia; however, the mechanism is unknown
Yoshida et al[404]	2017	4	Case report	Duloxetine 20 mg (n = 1)	Initial T&T olfactometer Threshold and identification and then 7 days after cessation of duloxetine	Duloxetine may cause worsened threshold and identification levels that improve on cessation of medication
Horger et al[405]	2016	5	Case report	Midodrine 5 mg 3 times daily (n = 1)	Clinical history	Self-reported dysosmia that improved on cessation of medication
Che et al[406]	2018	5	Case report	Metoprolol (n = 1)	Clinical history	Self-reported dysosmia that improved on cessation of medication

CT = computed tomography; ERP = event-related potential; LOE = level of evidence; MRI = magnetic resonance imaging; OC = olfactory cleft; OF = olfactory function; RCT = randomized controlled trial; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, identification; T&T = Toyoda and Takagi; UPSIT® = University of Pennsylvania Smell Identification Test.

The body of literature dedicated to medication-related changes in olfaction is of low quality and summarized in Table VII.8. Although many reports of olfactory loss following administration of medications are anecdotally described in large pharmaceutical databases,[394] there is increasing use of psychophysical olfactory testing used to describe the perturbations in olfaction. The drugs with the strongest data supporting the associations of decreased olfaction include zinc, tetrahydrocannabinol, remifentanil, and sildenafil.[395–397] 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.[391,398] Numerous other drugs are associated with reports of OD and include commonplace medications such as propofol, duloxetine, midodrine, metoprolol, local anesthetics, and oral antibiotics.[392,399–405] Meanwhile, there is some evidence that thyroid hormone modulation and α_{1A}-adrenoceptor antagonism may lead to olfactory improvements, although the clinical significance and mechanism of these findings are unknown.[406]

Although several studies have investigated the use of oral zinc supplementation to treat olfactory loss without overall convincing evidence that it can,[407] 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 OD, and ≈70 years later the topical administration of zinc gluconate was found to have similar effects.[408–412] 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

TABLE VII.8 Section evidence summary: Related to RT

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Álvarez-Camacho et al[425]	2017	2*	Systematic review	23 studies N = 13 to 1411 patients	OD 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[422]	2013	3	Cohort	14 patients with HNC whose treatment included high-dose RT to the OE 56 patients with HNC whose treatment included RT sparing the OE	SOIT	20 months after RT, patients with HNC treated with high doses to the OE had worsened odor thresholds and identification scores than those treated with low-dose RT
Galletti et al[426]	2016	4	Case-control	9 patients with NPC treated with RT and chemotherapy 9 HCs	Olfactory ERPs Hyposmia Rating Scale Olfactory VAS	Significant differences in the latency and amplitude of olfactory ERPs between patients and controls, correlating with subjective olfactory assessments
Gurushekar et al[419]	2020	3	Cohort	13 patients with HNC undergoing RT	CCCRC olfactory test Mucociliary clearance AHSP questionnaire	Decrease in objective OF during RT with improvement after 3 months, but persistent mucociliary dysfunction
Hölscher et al[421]	2005	3	Cohort	22 patients undergoing head and neck RT with a high dose to the OE 22 patients undergoing H&N RT with a low dose to the OE	SS-ID, SS-D, SS-T	During RT, there was 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 the OE ≥6 months post-RT
Jalali et al[430]	2014	3	Cohort study	54 patients with HNC or brain malignancy	n-Butanol threshold In vivo dosimetry	Reduced olfactory thresholds scores (elevated thresholds) 6 months after RT, with a dose-dependent response

(Continues)

TABLE VII.8 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Riva et al[420]	2019	3	Cohort	10 patients undergoing RT for HNC, excluding nasal tumors	SS-ID, SS-D, SS-T Nasal obstruction symptom score	Decrease in odor TDI scores during RT with recovery after 3 months; however, 40% with subjective persistent hyposmia
Riva et al[424]	2015	3	Cohort	30 HCs 30 patients with NPC treated with RT and chemotherapy	SS-ID, SS-D, SS-T Symptom survey	≥2 years post-RT, patients exhibited worsened odor threshold and TDI scores as compared with HCs No difference based on type of RT
Veyseller et al[427]	2014	4	Case-control	24 patients with NPC treated with RT ≥12 months ago 14 HCs	CCCRC olfactory test Olfactory bulb volume (MRI)	OF and OB size were significantly lower in patients following RT as compared with controls
Wang et al[423]	2015	3	Cohort	41 patients with NPC treated with intensity-modulated RT	UPSIT® TWSNOT-22	One year after completion of IMRT, mild OD still existed

AHSP = Appetite, Hunger and Sensory Perception; CCCRC = Connecticut Chemosensory Clinical Research Center; ERP = event-related potential; HC = healthy control; HNC = head and neck cancer; MRI = magnetic resonance imaging; NPC = nasopharyngeal cancer; OB = olfactory bulb; OD = olfactory dysfunction; OE = olfactory epithelium; OF = olfactory function; RT = radiation therapy; SOIT = Scandinavian Odor-Identification Test; SS-ID = Sniffin' Sticks identification only; SS-D, Sniffin' Sticks discrimination only; SS-T = Sniffin' Sticks thresholds only; TDI = thresholds, discrimination, and identification; TWSNOT-22 = Taiwanese version of the 22-item Sino-Nasal Outcome Test; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.
*Level of evidence (LOE) downgraded because of heterogeneity of results and lack of randomized controlled trials.

that medication usage of a wide array of both prescription and nonprescription medications may result in deficits of OF. Importantly, for otolaryngologists 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.[403,404,405]

Multiple medications can have detrimental effects on olfaction.

Aggregate grade of evidence: C (Level 2: three studies; Level 3: two studies; Level 4: seven studies; Level 5: two studies).

F | Postradiation Therapy

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.[413–415] A systematic review of 23 studies demonstrated impairment in odor detection, discrimination, and identification after RT.[416] 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 OF.[413,414] In a study of 70 patients, Bramerson et al[416] demonstrated that radiation dosage was significantly related to OD, while age, sex, and concurrent chemotherapy administration were not.[416] In a series of 56 patients, Hölscher et al[415] demonstrated that higher radiation doses to the OE were associated with lower odor discrimination scores 2 weeks after initiating RT, but no dose-dependent difference was observed for odor identification and threshold scores.[415]

Several investigators have demonstrated persistent objective OD over 1 year following the completion of RT. Such studies have utilized a variety of outcome metrics, including the UPSIT®, Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test, SS, and measurement of event-related potentials (ERPs) to assess odor threshold, discrimination, and identification (TDI),

suggesting that RT-induced OD is both qualitative and quantitative.[415–421]

Various mechanisms have been proposed regarding the pathophysiology of these observed changes, although there is limited evidence in their validation. Proposed mechanisms include direct cytotoxic damage to the OE, OB, or its supporting cells; impaired neurogenesis; treatment-induced obstruction of the OC; and decreased vascular perfusion to the OC. Murine models have demonstrated that ionizing radiation affects olfactory neurogenesis and OB plasticity.[422,423] Patients with nasopharyngeal cancer treated with RT have been shown to exhibit reductions in OBV on posttreatment MRI, measured ≥1 year after completion of therapy.[421]

Regarding prognosis, there appears to be a radiation dose-dependent effect on long-term OD.[415,416,424] However, individual outcomes may be unpredictable, as Jilali et al[424] demonstrated that the actual dose delivered to the nasal mucosa and OC is variable despite similar total radiation doses. This finding may explain some of the inconsistency in published outcomes of olfaction following RT.

Radiation to the olfactory system can lead to OD that is sometimes temporary but can be permanent in some patients.

Aggregate grade of evidence: C (Level 2: one study; Level 3: seven studies; Level 4: two studies).

G | Related to underlying systemic disease

1 | Autoimmune

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 Sjögren syndrome,[426–433] systemic sclerosis,[434,435] multiple sclerosis,[436–463] granulomatosis with polyangiitis,[464–468] systemic lupus erythematosus (SLE),[435,469–471] rheumatoid arthritis,[472] myasthenia gravis,[473–475] neuromyelitis optica,[476] Behçet disease,[477–479] and Mikulicz disease.[55] Studies have used different methodologies but associations with age, sex,[430,441,447,453] and mood disorders[429,434,435,440,441] have been observed. Association with disease activity,[427,435,437,441,442,444,445,447–450,452,453,457–460,462,467,468,470,471,473,474] neurological manifestations,[435,437–443,445,447,450,452,453,457–460,462,463,469] magnetic resonance imaging (MRI) abnormalities,[435,438,443,446,450,451,455,461,476,479] and autoantibodies[435,473,476,477] have been found in different autoimmune diseases. There are only four longitudinal studies, and therefore results regarding worsening or stabilization of OD are controversial.[435,457,460,462]

Autoimmune diseases are a potential cause of OD.

Aggregate grade of evidence: C (Level 2: one study; Level 4: 55 studies).

2 | Vitamin-mineral deficiency

Vitamins 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.[479] As a result, it has been considered an important element when maintaining OF. Deficiency in this trace metal has been linked with anosmia, but excess has also been associated with toxic effects on the olfactory system.[479,480] Mechanisms for the latter include inhibition of glutathione reductase, induction of necrosis, impairment of the electron transport chain, and dysregulation of copper or calcium homeostasis.[480,481,482] Furthermore, deficiencies in copper and nickel can produce similar smell alterations when assessing receptor response profiles.[479]

The OR neurons primarily use glutamate, a neurotransmitter, during the excitation phase. Concentration variations can cause oxidative stress, as shown in AD, and can occur secondarily to low vitamin E levels. These alterations in concentrations can ultimately lead to shifts in smell sensation.[483,484,485]

The mechanism for regeneration of the OE is not entirely clear, although 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.[479,486,487]

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, although no difference in treatment.[479,488]

As shown through the importance of multiple vitamins and minerals, ultimately malnutrition can have a significant negative effect on 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 OD, there is no high-level data to currently prove this.

TABLE VII.9 Section evidence summary: Related to autoimmune disease

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
SS	Al-Ezzi et al[431]	2017	2	Systematic review with meta-analysis	378 patients with primary SS compared with HCs	Standard mean deviation of olfcactory ability from normal	The impact of primary SS on patients vs HCs was: smell standard mean deviation 0.78 (95% CI, 1.29–0.27)
	Henkin et al[432]	1972	4	Cross-sectional	29 patients with SS and 10 patients with various other diseases of the parotid glands	Detection and recognition thresholds for pyridine, nitrobenzene, and thiophene	45% with hyposmia Cyclophosphamide improved smell function
	Jones et al[433]	1974	4	Case-control	14 female patients with SS and 16 controls	Forced-choice three-stimulus sniff technique	All patients with SS had hyposmia, inflammatory changes in the nasal mucous membrane, and nasal accumulation of ^{99m}technetium pertechnetate
	Weiffenbach and Fox[434]	1993	4	Case-control	30 patients with SS and 16 HCs	UPSIT®	Patients with SS scored worse than controls. The lower score of the patients showed a significant depression of olfactory sensitivity
	Kamel et al[435]	2009	4	Case-control	28 patients with SS and 37 HCs	UPSIT®	SS patients scored worse than HCs Taste and smell thresholds were correlated Association with reduced QOL
	Midilli et al[436]	2013	4	Case-control	77 patients with SS and 77 HCs	5 component smell discrimination test	SS patients scored the same as controls Smell disorder was associated with nasal polyposis
	Su et al[437]	2015	4	Case-control	15 patients with SS and 32 patients with burning mouth syndrome used as controls	SS-TDI	Olfactory scores were the same between SS and burning mouth syndrome groups
	Rasmussen et al[438]	1986	4	Case-control	36 patients with SS and 36 controls	Elsberg olfactometer	No difference between groups was shown No correlation with mucociliary clearance

(Continues)

TABLE VII.9 (Continued)

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
SSc							
	Amital et al[439]	2014	4	Case-control	20 patients with SSc and 21 controls	SS-TDI	3 of 20 (15%) patients had SSc hyposmia TDI SSc < controls TDI scores correlate inversely with BDI-II
	Bombini et al[440]	2018	4	Case-control	143 patients with SLE, 57 with SSc, and 166 HCs	SS-TDI, MoCA, BAI, BDI, MRI, (anti-P) antibodies	OD was seen in 54.5% of patients with SLE, 59.3% with SSc, and and 14.45% of HCs SLE and SSc TDI < HCs. OD was associated with age, inflammation, and hippocampus and amygdala volume In patients with SLE, there was an association with anti-P, anxiety, and depression symptoms
MS	Ansari et al[441]	1976	4	Case-control	40 patients with MS and 24 controls	Amyl acetate and nitrobenzene double-blind threshold tests	Patients with MS patients had no detectable olfactory deficit compared with controls No correlation was seen between visual and olfactory involvement
	Samkoff et al[442]	1996	4	Case-control	16 patients with MS and 14 controls	UPSIT®	Patients with MS scored the same as controls Negative correlation between UPSIT® scores and EDSS
	Doty et al[443]	1997	4	Case series	26 patients with MS	UPSIT® MRI with gadolinium	38.5% of patients with MS had olfactory loss Negative correlation with lesion load
	Hawkes et al[444]	1997	4	Case-control	72 patients with MS and 96 controls	UPSIT® Olfactory-evoked potentials	15% patients had abnormal UPSIT® 25% patients had abnormal olfactory-evoked potentials UPSIT® scores correlated with EDSS UPSIT® scores with the H2S-evoked response

(Continues)

TABLE VII.9 (Continued)

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Zivadinov et al[445]	1999	4	Case-control	73 patients with MS and 40 controls	B-SIT and clinical variables	12.5% patients with MS had an absolute loss of smell Borderline normal in 10% and abnormal in 12.5% Correlations between smell identification score and symptoms of anxiety, depression, and severity of neurological impairment
	Zorzon et al[446]	2000	4	Case-control	40 patients with MS and 40 controls	B-SIT	12.5% of patients had abnormal olfactory B-SIT MS score was worse than in controls Sex, age, disease duration, disability, anxiety, depression, lesion load Correlation between B-SIT score and olfactory brain lesion load, and negative correlation EDSS
	Fleiner et al[447]	2010	4	Case-control	16 patients with MS and 16 controls	SS-TDI	MS: 50% hyposmia EDSS score was inversely correlated with the identification subtest
	Goektas et al[448]	2011	4	Cross-sectional, case-control	36 patients with MS and 36 controls	SS-TDI	44.4% of patients with MS had olfactory alteration OBV correlated with OF Identification scores correlated with neurological scores
	Lutterotti et al[449]	2011	4	Case-control	50 patients with MS and 30 controls	SS-TDI	Patients with MS scored worse than controls on TDI, threshold, and identification Worsened smell threshold earlier in disease and then impaired identification with widespread chronic disease

(Continues)

TABLE VII.9 (Continued)

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Dahlslett et al[450]	2012	4	Case-control	30 patients with MS and 30 controls	Olfactory ERP SS-TDI	Patients with MS scored worse on TDI Olfactory ERP 23.8% hyposmia TDI 40% hyposmia TDI score inversely correlated with EDSS score Identification inversely correlated with disease duration and EDSS
	Erb et al[451]	2012	4	Case-control	30 patients with MS and 30 controls	SS-TDI	Threshold and discrimination scores were similar between patients with MS and controls, whereas total TDI and identification values were poorer in patients with MS No correlation between fractional anisotropy reduction in lesions and the EDSS or the TDI score Identification: correlation with fractional anisotropy values of lesions in the olfactory brain
	Silva et al[452]	2012	4	Case-control	153 patients with MS and 165 controls	B-SIT	Patients with MS scored worse on B-SIT compared with controls Age, disease duration, education, EDSS, depression, and MMSE
	Rolet et al[453]	2013	4	Case series	50 patients with MS	SS-TDI	OD 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

(Continues)

TABLE VII.9 (Continued)

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Caminiti et al[454]	2014	4	Case-control	30 patients with MS and 30 controls	Olfactory ERP	7 of 30 patients did not show Olfactory ERP 16 of 23 patients had amplitude significantly lower than in the control group
	Erb-Eigner et al[455]	2014	4	Case-control	30 patients with MS and 12 controls	SS-TDI	Patients with MS scored worse than controls TDI score increased with decreased fractional anisotropy, increased mean diffusivity, and increased radial diffusivity Fractional anisotropy decreased in olfactory structures TDI correlated with EDSS
	Holinski et al[456]	2014	4	Case series	20 patients with MS	Olfactometer	25% hyposmic. Negative correlation of OBV and hydrogen sulfide latencies Hyposmic patients had smaller OBVs and higher volume of lesions in the OB
	Caglayan et al[457]	2016	4	Case-control	29 patients with MS and30 controls	SS-TDI	Patients with MS had worse thresholds compared with controls Threshold, identification, and TDI correlated with age TDI correlated with MMSE and EDSS
	Jordy et al[458]	2016	4	Case-control	100 patients with MS and 100 controls	CCCRC olfactory test	Olfactory alteration was seen in 32% of patients with MS compared with 3% controls
	Kandemir et al[459]	2016	4	Case-control	20 patients with MS and 20 controls	B-SIT	No difference in total smell scores and disease duration or relapse

(Continues)

TABLE VII.9 (Continued)

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Li et al[460]	2016	4	Case-control	26 patients with MS and 26 controls	T&T olfactometer	42.3% had olfactory impairment but there was no difference between MS and control groups T&T correlated with EDSS OB was smaller in patients with OD
	Good et al[461]	2017	4	Case-control	73 patients with MS and 73 controls	UPSIT® ODT	Patients with MS scored worse than controls on the UPSIT® ODT correlation with lesion volume
	Uecker et al[462]	2017	4	Case series	20 patients with MS	SS-TDI	50% hyposmia No significant change during follow-up Discrimination correlated negatively with number of relapses VAS correlated with the TDI score of the longitudinally tested patients
	Atalar et al[463]	2018	4	Case-control	31 patients with MS and 24 controls	CCCRC olfactory test	Smell identification, smell threshold, and mean olfactory scores were all worse compared with controls Disease duration and and number of MS attacks and CCCRC scores were inversely correlated MOCA test scores and CCCRC scores/subscores were positively correlated
	Bsteh et al[464]	2018	4	Case-control	Relapse group: 28 patients with MS Stable group: 27 patients with MS as controls	SS test (only threshold)	Olfactory threshold was impaired in patients with acute MS relapse Relapse group MS EDSS < controls
	Ciurleo et al[465]	2018	4	Case series	30 RRMS	CCCRC olfactory test	MS olfactory alterations were related to disability progression and disease activity

(Continues)

TABLE VII.9 (Continued)

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Li et al[466]	2018	4	Case-control	37 patients with NMO and 37 patients with MS	T&T olfactometer, gray matter voxel-based morphometryand MRI	Olfactory deficits: 51.4% in patients with NMO and 40.5% in patients with MS Patients with NMO with OD had OBs larger than patients with MS with OD
	Bsteh et al[467]	2017	4	Case-control	128 patients with relapsing remitting MS and 9 patients with progressiveMS	SS-TDI	Discrimination and identification worsened over 3 years Threshold impairment was transient and predicted inflammatory disease activity, while identification and discrimination were associated with disability progression
	Carotenuto et al[468]	2019	4	Cross-sectional, case-control	55 patients with MS and 20 controls	UPSIT®	Worsened score compared with controls Scores on the SDMT, CVLT-II, BVMT, and COWAT were related to olfactory test score
GPA	Göktas et al[469]	2010	4	Case series	9 patients with GPA	SS-TDI	Patients with GPA had OD
	Laudien et al[470]	2009	4	Case series	76 patients with GPA	SS-TDI	14 (18.4%) with OD
	Fasunla et al[471]	2012	4	Case-control	16 patients with GPA and 16 controls	SS-TDI	Patients with GPA scored worse than controls
	Proft et al[472]	2014	4	Case-control	44 patients with GPA and 44 controls	SS-TDI	Patients with GPA scored worse in all domains compared with controls, with 75% hyposmia Discriminationn: lower scores with azathioprin
	Zycinska et al[473]	2016	4	Case series	43 patients with GPA	SS-TDI	74% of patients with GPA had OD, scoring below normal on TDI and all domains

(Continues)

TABLE VII.9 (Continued)

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
SLE	Cavaco et al[474]	2012	4	Case-control	85 patients with SLE and 85 controls	B-SIT	Patients with SLE and neuropsychiatric SLE scored worse on B-SIT compared with controls Greater OD in patients with neuropsychiatric SLE than controls or nonneuropsychiatric SLE patients
	Chen et al[475]	2019	4	Case-control	65 patients with SLE and 50 controls	CCCRC olfactory test	OD was correlated with SLE disease activity and presence of anti-P antibodies
	Bombini et al[440]	2018	4	Longitudinal case-control	143 patients with SLE, 57 patients with SSc, and 166 HCs	SS-TDI, MoCA, BAI, BDI, MRI, (anti-P) antibodies	OD was seen in 54.5% of patients with SLE, 59.3% of patients with SSc, and 14.45% of HCs OD was associated with age, inflammation, and smaller hippocampi and amygdalae volumes In patients with SLE, OD was associated with anti-P antibodies and anxiety and depression symptoms
	Shoenfeld et al[476]	2009	4	Case-control	50 patients with SLE and 50 controls	SS-TDI	Patients with SLE scored worse on TDI than controls
Rheumatoid arthritis	Steinbach et al[477]	2011	4	Cross-sectional, case-control	111 patients	SS-TDI	Patients with rheumatoid arthritis scored worse on overall TDI and threshold compared with controls No correlation with disease activity, severity, extra-articular manifestations, or autoantibodies
Myasthenia gravis	Leon-Sarmiento et al[478]	2012	4	Cross-sectional, case-control	27 patients with myasthenia gravis, 11 patients with polymiositis,and 27 HCs	UPSIT®	Patients with myasthenia gravis UPSIT® < HCs Patients with polymiositis UPSIT® < HCs

(Continues)

TABLE VII.9 (Continued)

Disease	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Tekeli et al[479]	2015	4	Case-control	30 patients with myasthenia gravis and 30 controls	SS-TDI	Patients with myasthenia gravis showed significantly lower olfactory and gustatory scores than controls Olfactory loss correlated with severity of the disease
	Leon-Sarmiento et al[480]	2013	4	Literature review January 1950 through December 2012	Case reports	NA	Myasthenia gravis was associated with olfactory impairment
Neuromyelitis optica	Zhang et al[481]	2015	4	Case-control	49 patients with neuromyelitis optica and 26 controls	T&T olfactometer	Neuromyelitis optica spectrum disorders: 53% of patients with OD had smaller OBVs than patients without it or controls Both detection and recognition thresholds for olfaction were negatively correlated with OBV
BD	Veyseller et al[482]	2014	4	Case-control	30 patients with BD and 30 controls	CCCRC olfactory test	Patients with BD scored worse than controls
	Akyol et al[483]	2016	4	Case-control	50 patients with BD and 46 controls	SS-TDI	Patients with BD scored worse on TDI and identification domains compared with controls
	Doğan et al[484]	2017	4	Case-control	16 patients with BD and 16 controls	CCCRC olfactory test	Patients with BD scored worse than controls Parenchymal involvement led to worse scores
Mikuliczs disease	Takano et al[485]	2011	4	Case series	44 patients with Mikuliczs disease	T&T olfactometer	45% of patients had olfactory abnormalities Association of IgG4-positive plasmacytes in the nasal mucosa with olfactory abnormalities

B-SIT® = Brief Smell Identifiation Test; BAI = Beck Anxiety Inventory; BD = Behçet disease; BDI = Beck Depression Inventory; BVMT = Brief Visuospatial Memory Test; CCCRC = Connecticut Chemosensory Clinical Research Center; CI = confidence interval; COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test-II; EDSS = Expanded Disability Status Scale; ERP = event-related potential; GPA = granulomatosis with polyangiitis; HC = healthy control; LOE = level of evidence; MMSE = Mini-Mental Status Examination; MRI = magnetic resonance imaging; MoCA = Montreal Cognitive Assessment; MS = multiple sclerosis; NA = not available; NMO = neuromyelitis optica; OB = olfactory bulb; OBV = olfactory bulb volume; OD = olfactory dysfunction; ODT = odor detection threshold; OF = olfactory function; PMS = progressive multiple sclerosis; SDMT = Symbol Digit Modalities Test; SLE = systemic lupus erythematosus; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; QOL = quality of life; RRMS = relapsing-remitting multiple sclerosis; SS = Sniffin' Sticks; SSc = systemic sclerosis; T&T = Toyoda and Takagi; TDI = threshold, discrimination, identification; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

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, experience smell deviations following damage to the arcuate nucleus and ventromedial nuclei of the hypothalamus.[490] Subsequent lack of hormone secretion from the anterior pituitary causes delay in normal puberty and its associated features.[490,491]

The pituitary gland itself, while crucial in various homeostatic functions, also plays an important role in olfaction. Endocrinologic manifestations of Cushing syndrome can include inappropriate antidiuretic hormone secretion, catecholamine secretion, hyperprolactinemia, and adrenocorticotropic hormone secretion. There is the potential for the subsequent symptoms associated with these derangements to include anosmia.[491] On the other hand, patients with adrenocortical insufficiency (at times secondary to a pituitary cause), also called Addison disease, have a decreased ability to recognize odors. This is primarily related to the effects of hormonal reduction on smell function, but also attributed to the actions of those hormones on stem cells in the OE, which induce maturation and differentiation.[492,493] Acromegaly and gigantism, secondary to hypersecretion of growth hormone and, in turn, insulinlike growth factor 1, are chronic, progressive, multisystem diseases. Part of the spectrum of clinical features can include hyposmia or anosmia. It is also worth noting that patients with de Morsier syndrome, septo-optic dysplasia, can have symptoms of anosmia secondary to pituitary variability.[490,494]

Patients with hypothyroidism have similar impairments in smell recognition secondary to deficient hormonal effects on the olfactory organ, and, by treating primary hypothyroidism, olfactory ability can improve.[495,14]

Other deviations resulting in olfactory variations can affect the OB and receptor environment. Kallman syndrome, otherwise known as hypogandotrophic hypogonadism, is an X-linked neuronal migrational disorder that causes anosmia secondary to aplasia of the OB.[496,497] Turner syndrome shares some parallel symptomology to Kallman syndrome, including OD, but with markedly different etiology.[498] As noted in the section above, patients with Sjögren syndrome can experience excessive dryness of the nasal mucosa, as evidenced in atrophic rhinitis, with resultant OD secondary to loss of moisture within the receptor environment. This ultimately leads to diminished chemoreception and transduction and effects on the hypothalamic-pituitary-adrenal axis.[490,110] 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 only temporary until the time of delivery.[500]

Finally, a combination of the secondary neurodegeneration and microvascular disease associated with diabetes mellitus (DM) results in a significant proportion of patients with DM experiencing diminished smell sensation.[501,502] Although this can be gradual in onset, and often undetected, there seems to be no correlation between DM duration and prevalence of OD.

Underlying endocrine disorders can affect the functionality of the olfactory system.

Aggregate grade of evidence: C (Level 3: four studies; Level 4: four studies; Level 5: three studies).

4 | Renal failure

Our systematic literature review identified that patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) commonly experience olfactory impairment—a finding consistent with narrative reviews by Raff et al,[503] Landis et al,[504] and recently by Robles-Osorio et al.[505] 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,[503,504,506] and OD correlates with the severity of kidney disease.[507,508] Odor discrimination is also diminished in renal patients.[506,509–511] Results concerning odor detection threshold in these patients are conflicting, describing either no change[506,512,513] or significant impairment.[508] Most early studies, however, had sample size limitations.[504,509–511]

Recently, Koseoglu et al[514] reported impaired odor identification, discrimination, and threshold in non-DM 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[515] reported odor identification impairment in most patients with CKD (≈70%) and ESKD (≈90%). Detection threshold was comparable between patients with CKD and control participants, but higher in patients with ESKD.

Proposed explanations for olfactory impairment in renal patients[508] range from accumulation of uremic toxins impairing olfaction[516,517] or inducing polyneuropathy,[518]

TABLE VII.10 Section evidence summary: Related to endocrine diseases

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Gleeson et al[496]	2011	5	EBR	Medline search using olfaction, smell, anosmia, dysosmia, phantosmia, odor identification, odor threshold, odor discrimination, OE, OB, and UPSIT®	Multiple psychometric measure of smell	Several endocrine disorders evidence disorders of smell
Sykiotis et al[497]	2010	4	Retrospective cohort	90 men with idiopathic hypogonadotropic hypogonadism undergoing long-term pulsatile gonadotropin-releasing hormone treatment	Subjective smelling ability	Patients with idiopathic hypogonadotropic hypogonadism with anosmia, Kallmann syndrome, 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[498]	1966	4	Prospective case-controlled	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[500]	1970	4	Case series	7 cases of patients with de Morsier syndrome	Subjective smelling ability	All patients had hypogo-nadotrophic hypogonadism with anosmia
McConnell et al[501]	1975	3	Prospective cohort	15 patients with untreated primary hypothyroidism assessed pretreatment and posttreatment with thyroxine	Threshold and recognition olfactory testinh	Taste and smell defects are common clinical abnormalities in patients with primary hypothyroidism These defects may contribute to the anorexia and lack of interest in eating, which are frequently observed

(Continues)

TABLE VII.10 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Stamou et al[502]	2018	5	Literature review of Kallman syndrome	Patients with IGD	NA	The clinical spectrum of IGD includes a variety of disorders including Kallmann syndrome, ie, 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[504]	2012	3	Cohort, controlled	30 patients with Turner syndrome, 14 age-matched patients with other congenital hypogonadisms, and 43 age-matched HCs	BAST-24 olfactory testing	Patients with Turner syndrome show impairment of smell but not of taste, compared with those with other congenital hypogonadisms as well as HCs taking contraception
Kamel et al[505]	2009	3	Cohort-matched, prospective, cross-sectional	28 patients with Sjögren syndrome and 37 matched controls	Following administration of smell and taste testing, and completion of QOL assessment	Several endocrine abnormalities may play a role in the development of primary Sjögren syndrome, with abnormal hypothalamic-pituitary-adrenal axis seen in a fifth of patients and hypothyroidism seen in many patients Impairment of chemosensory perception occurred in the Sjögren syndrome group compared with age- and sex-matched controls

(Continues)

TABLE VII.10 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Cameron[506]	2014	5	Literature review of the 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[507]	2017	4	Cross-sectional	3151 total NHANES participants with no DM, DM conservatively managed, DM controlled with oral medication, or DM controlled with insulin	Following collection of data regarding self-reported OF	Among patients with DM, there was a significant trend to severe hypos-mia/anosmia No association was observed between DM duration and prevalence of OD
Brady et al[508]	2013	3	Cohort	19 HCs 19 patients with noncomplicated DM 15 patients with DM and neuropathy without neuropathic pain 21 patients with DM and neuropathy and neuropathic pain	SS-TDI	Patients with DM score worse on olfactory testing compared with controls, but only in groups with peripheral neuropathy Severity of neuropathy or neuropathic pain did not correlate with severity of OD
Deniz et al[509]	2016	2	RCT	Patients with primary hypothyroidism and 31 HCs	SS-TDI	Patients with primary hypothyroidism had olfactory deficits at baseline Their olfaction significantly improved after treatment with L-thyroxine at 3 months

BAST-24 = Barcelona Smell Test-24; EBR = evidence-based review; HC = healthy control; IGD = isolated gonadotropin-releasing hormone deficiency; LOE = level of evidence; NA = not available; NHANES = National Health and Nutrition Examination Survey; OB = olfactory bulb; OD = olfactory dysfunction; OF = olfactory function; OE = olfactory epithelium; QOL = quality of life; RCT = randomized controlled trial; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

to nutrient removal by dialysis impairing regeneration and renewal of olfactory cells.[511] Despite uremia being a previously accepted widespread explanation,[517] Raff et al[503] found no correlation between accumulated uremic toxins and impaired olfaction in patients with ESKD. Notably, this olfactory impairment appears to be physiologically reversible.[519] Improving olfaction in kidney transplant recipients also attests to the reversibility of ESKD-associated olfactory losses.[508]

Earlier studies reported that kidney patients are unaware of their disease-associated olfactory decline.[504,506,520] Self-assessments of smell and taste are similar in controls and patients with CKD or ESKD, despite significant differences on formal testing in identification among them and in threshold between CKD and ESKD[13]—not surprisingly for mild hyposmia.[521,522] However, many patients do complain that the smell and taste of food are less pleasant than before renal impairment.[511,512,523,22]

Reports on the effect of dialysis on olfactory losses are inconsistent,[517] ranging from improvement after hemodialysis,[513] or no change,[508] to a slight worsening of olfaction.[509,510] Further assessments in larger numbers of patients are required.

H | Related to sinonasal or intracranial tumor

Sinonasal or intracranial neoplasms may lead to OD 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 OC and neuroepithelium.[524] Neurosensory deficits reflect damage or dysfunction to the olfactory neural pathway, typically from tumor involvement of the OE or OB or higher processing centers such as the prefrontal or temporal lobe.[525–528]

Sinonasal tumors, such as squamous cell carcinoma, inverted papillomas, and esthesioneuroblastomas, often present with unilateral more than bilateral symptoms.[526,529–532] Esthesioneuroblastomas, also known as olfactory neuroblastomas, which originate from the basal progenitor cells within the olfactory neuroepithelium, can present with nasal airway obstruction, epistaxis, and/or olfactory disturbances.[529,530] 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 caused by their compression or invasion of the olfactory nerves.[532–535]

Iatrogenic interventions within the nose for sinonasal or intracranial tumor extirpation can cause both transient and permanent olfactory loss.[536,537] The disturbance in OF from surgery can occur through four means: mechanical injury, airflow modification, vascular/neural injury, and other.[524,531] 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, such as scarring, which prevent airflow to the OC and mucosa. Additionally, transient hyposmia may occur as a result of postoperative edema or packing. Vascular injury arises from iatrogenic ischemia to the OE, while neural compromise may stem from a postoperative infection. Other mechanisms include medications and general anesthesia.[524,531,538]

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.[524,539,540] Contemporary endoscopic approaches have been shown to preserve OF when compared with traditional transseptal microscopic approaches.[541,542] However, expanded endonasal approaches may have a higher risk of olfactory injury when compared with limited transsphenoidal approaches.[524]

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.[539,540,543–547] 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 OC and OB has been proposed to assist with smell preservation.[548,549]

I | Related to increasing age

OD has a well-established association with advancing age. A systematic review and meta-analysis of 25 individual studies, including 175,073 healthy individuals with a mean age of 63.5 years (range, 18–101 years), cites an overall population prevalence of 22.2%.[524] This rate rises to 34.5% in studies with a mean age >55 years compared with 7.5% in studies with a mean age <55 years. Another meta-analysis using effect size identifies that the most significant decrease in olfaction begins in the fifth decade of life.[525] The odds ratio for hyposmia ranged from 1.06 to 1.79 for every 5-year increment in age.[526–528] Individual cross-sectional studies have found rates of hyposmia in

13.9% to 50% of individuals >65 years and up to 80% in those >80 years.[529–535] Longitudinal studies have supported the findings of cross-sectional studies with one citing an overall 5-year incidence of developing OD in 12.5% of previously normosmic older adults, ranging from 4.1% in those aged 53 to 59 years and up to 47.1% in those aged 80 to 97 years.[527] 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.[527,536–539]

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 <10 years is worse than teenagers and adults, likely related to either underdeveloped cognitive processing or difficulty in testing methodology in this age group, and improves through the second decade of life.[540,541] While some studies have suggested that odor detection thresholds 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 third to fourth decade of life followed by slow steady deterioration that accelerates after age 60 years and becomes particularly severe after age 70 to 80 years.[524,528,529,533,540–549] Notably, 5-year mortality rates in these hyposmic elderly individuals has been found to be as much as 36% higher compared with their normosmic counterparts, highlighting clinical significance.[531,535,550]

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 ORs; 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.[531,536,551–553] The OB may demonstrate atrophy, loss of neuronal elements, and decreased laminae and glomeruli with age, as well as accumulation of tau and α-synuclein.[531,536,554,555] 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, OFC, anterior olfactory sulcus, and cholinergic system.[531,536,538,556] Some studies suggest a decline in the trigeminal contribution to olfaction may play a role, although this is unconfirmed.[538] Genetic predispositions exist for age-related hyposmia, including the val66met polymorphism of brain-derived neurotrophic factor and the ε4-allele of human apolipoprotein E gene.[531] Despite the contribution of genetics, which has been shown to influence the intensity and perception of olfaction, twin studies suggest that environmental factors likely contribute to a greater degree than genetic factors with increased age.[553,557]

While broad age-related trends are well-established, significant heterogeneity exists between study findings because of 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.[546] 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.[524,529,531,535,538,545,558,559] Sensitivity can be improved by querying specifically about age-related changes in smell function.[560]

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 of this common and important problem.

Increasing age after the fourth decade is associated with decreasing OF.

Aggregate grade of evidence: B (Level 1: two studies; Level 2: 27 studies).

J | Related to neurodegenerative disease

Over the past decade, multiple studies have demonstrated that OD may be the earliest sign of neurodegeneration, affecting those with subjective cognitive decline, mild cognitive impairment (MCI), AD, and Parkinson disease (PD).

In preclinical AD, patients can experience subjective cognitive decline that causes them concern, although classic neuropsychological tests are not able to detect any change in cognition at this time.[586–916] A meta-analysis of five studies evaluating OF in individuals with

TABLE VII.11 Section evidence summary: Related to aging

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Desiato et al[558]	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 brief identification tests give better information
Zhang et al[559]	2017	1	Meta-analysis (13 studies)	Healthy adults: aged 30–39.9 years vs those 40–49.9 years and those aged 35–55 years vs >55 years	Objective (UPSIT®, SS, BAST-24, B-SIT®)	OD on average starts in the fifth decade of life
Adams et al[592]	2017	2	Cross-sectional	NSHAP respondents	Subjective and objective (OFFE)	Decreased subjective recognition of OD with age
Brämereson et al[563]	2004	2	Cross-sectional	Adult inhabitants of Skövde, Sweden	Objective (SOIT)	OD overall prevalence 19.1%, increases with age
Hoffman et al[569]	2016	2	Cross-sectional	NHANES respondents	Subjective and objective (PST®)	OD overall prevalence 12.4%, and 39.4% in patients ≥80 years, poor sensitivity of self-report
Hummel et al[578]	2007	2	Cross-sectional	Healthy children in Dresden, Germany	Objective (SS-TDI), ERPs)	Children progressively attach more meaning to odors with age, improving identification
Kern et al[583]	2014	2	Cross-sectional	NSHAP respondents	Subjective and objective (OFFE)	OD increases with age and male sex
Larsson et al[582]	2000	2	Cross-sectional	Adult Swedish Twin Registry respondents	Objective (National Geographic Smell Survey)	Odor detection and identification impaired with age
Liu et al[560]	2016	2	Cross-sectional	NHANES respondents	Objective (PST)	OD overall prevalence 13.5%, increases with age and higher in men
Masala et al[581]	2018	2	Cross-sectional	Adult participants in Sardinia, Italy	Objective SS-TDI	Smell loss notable in patients >55 years
Mullol et al[579]	2012	2	Cross-sectional	Newspaper readers in Catalonia, Spain	Subjective and objective (proprietary 4 scent test)	Odor detection declines with age, but recognition and identification increases up to the 4th decade and declines after the 6th
Noel et al[562]	2017	2	Cross-sectional	NHANES respondents	Subjective and objective (PST®)	Increased OD with age, male sex, minority status
Oleszkiewicz et al[575]	2019	2	Cross-sectional	Healthy adults and children (multicenter)	Objective (SS-TDI)	Best performance at 20 to 30 years, worst performance <10 and >70 years

(Continues)

TABLE VII.11 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Pinto et al[573]	2014	2	Cross-sectional	NSHAP respondents	Objective (OFFE)	Black patients have worse OD compared with other races in peer age groups after correcting for confounders
Rawal et al[594]	2016	2	Cross-sectional	NHANES respondents	Subjective	OD prevalence increases with age (32% in patients >80 years)
Rawson et al[586]	2012	2	Cross-sectional	Healthy volunteers in Philadelphia, PA	Objective (scent thresholds for 2 odors, olfactory biopsies with fluorescence imaging)	Loss of OSN specificity with age
Sama-ul-Haq et al[588]	2008	2	Cross-sectional	Cadaver study	Mitral cell number and diameter	Number and diameter of mitral cells decreases with age
Schubert et al[564]	2012	2	Cross-sectional	Beaver Dam Offspring Study participants	Subjective and objective (SDOIT)	OD 0.6% in patients <35 years compared with 13.9% in patients >65 years
Schubert et al[577]	2017	2	Cross-sectional	EHLS adult participants	Objective (OLFACT-RL)	ODT worse in older adults
Segura et al[490]	2013	2	Cross-sectional	Healthy older adults in Barcelona, Spain	Objective (UPSIT®, MRI of olfactory centers)	Age-related OD accompanied by characteristic degenerative cortical changes
Sorokowska et al[574]	2015	2	Cross-sectional	Healthy volunteers (multicenter)	Subjective and objective (SS-ID)	Higher OD in patients <20 years and >60 years
Wilson et al[584]	2011	2	Longitudinal population-based	Elderly volunteers in Chicago, IL	Objective (B-SIT®), mortality	OD associated with increased mortality
Xu et al[576]	2020	2	Cross-sectional	NSHAP respondents	Objective (SS-ID, 5 odors)	Odor sensitivity and identification both decrease with age, identification more affected by cognition
Yousem et al[589]	1998	2	Cross-sectional	Healthy volunteers in Philadelphia, PA	Objective (UPSIT®, MRI of olfactory centers)	OB and tract volume increase up to fourth decade then decrease, but not correlated with UPSIT®
Doty et al[567]	1984	2	Cross-sectional	Healthy volunteers in Philadelphia, PA	Objective (UPSIT®)	Best olfactory performance between 20 and 40 years, high rates of anosmia in the elderly
Hoffman et al[569]	2006	2	Cross-sectional	NHIS respondents	Subjective	Increased risk for OD in patients >55 years

(Continues)

TABLE VII.11 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Murphy et al[568]	2002	2	Cross-sectional	EHLS adult participants	Subjective and objective (SDOIT)	Overall OD prevalence 24.5%, in patients >80 years 62.5%, accuracy of self-report worsens with age
Schubert et al[561]	2011	2	Longitudinal population-based	EHLS adult participants	Objective (SDOIT)	Incidence of OD increases with odds ratios of 1.78 for every 5-year increment of age
Sulmont-Rossé et al[571]	2015	2	Cross-sectional	Aupalesens project participants	Objective (ETOC, proprietary discrimination tests)	Link between caregiver dependence and OD independent of age

BAST-24 = Barcelona Smell Test-24; B-SIT = Brief Smell Identification Test; ETOC = European Test of Olfactory Capabilities; EHLS = Epidemiology of Hearing Loss Study; ERP = event-related potential; LOE = level of evidence; MRI = magnetic resonance imaging; NHANES = National Health and Nutrition Examination Survey; NHIS = National Health Interview Survey; NSHAP = National Social Life, Health, and Aging Project; OB = olfactory bulb; OD = olfactory dysfunction; ODT = odor detection threshold; OFFE = Olfactory Function Field Exam; OLFACT-RL = Osmic Enterprises Olfactometer; OSN = olfactory sensory neuron; PST = Pocket Smell Test; SDOIT = San Diego Odor Identification Test; SOIT = Scandinavian Odor Identification Test; SS = Sniffin' Sticks; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

subjective cognitive decline and in healthy older adults found that there was a significant difference, with slight relative impairment in patients with subjective cognitive decline.[710]

In the Mayo Clinic Study of Aging, participants were classified as having normal cognition, amnestic MCI, nonamnestic MCI, or dementia. This population-based prospective cohort study found that olfactory impairment is associated with amnestic MCI and the progression of amnestic MCI to AD dementia.[680]

A quantitative meta-analysis was performed on 31 previous studies including the one above comparing OF in patients with MCI and healthy older adults. This also found that olfactory deficits are present and robust in patients with MCI compared with healthy older adults, and that the most prominent alteration appears to be in olfactory identification scores.[688]

The association between smell loss and PD has long been known, but the ability to predict the development of PD using OF as a predictor has only been studied more recently. A systematic review and meta-analysis was published in 2019 evaluating the use of hyposmia as a predictive factor for PD. Of 1774 studies retrieved in the authors' search, only seven met requirements for inclusion. Inclusion requirements were a prospective human study, baseline olfactory test before any diagnosis of PD, reported relative risks, odds ratios, and hazard ratios with 95% confidence intervals 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 with normosmia.[907]

Interestingly, a recent meta-analysis also attempted to compare the OF deficits between patients with AD and those with PD 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 patients with PD compared with patients with AD.[859]

Although AD and PD are two of the most common and widely known types of dementia, there are several others. OD 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.[916] Lewy body dementia and rapid eye movement sleep behavior disorder, now suspected as a potential prodrome to Lewy body dementia and PD, have also both been associated with olfactory deficits, but only in smaller and lower LOE studies thus far.[866,874] As more subtypes of dementia emerge, it is likely that OF may predict these as well, as the olfactory system appears to be the "canary in the coal mine" of neurocognitive ability.

Cognitive testing in older patients with olfactory deficits.

Aggregate grade of evidence: A (Level 1: four studies; Level 2: seven studies; Level 3: 57 studies; Level 4: 265 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 with peer age groups, as some diminution of ability in both respects is expected with the normal aging process.

K | Related to other neurotransmitter disease states (eg, depression, schizophrenia, and autism)

The olfactory sensory neural pathway includes numerous brain regions implicated in the pathophysiology of a number of developmentally mediated neuropsychiatric disorders.[919–944] Notably, in the past two decades, the literature concerning psychophysical OF 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, (2) autism spectrum disorder (ASD), (3) obsessive-compulsive disorder (OCD), and (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 OD in patients with schizophrenia, with diffuse impairments among a wide variety of olfactory tasks being evident.[945–29] Results revealed moderate to large olfactory deficits in patients with schizophrenia, although significant heterogeneity was observed. Deficits among 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. Of these five olfactory domains, among individuals with schizophrenia: (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 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*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[944,30] concerning olfactory processing in ASD reveals a generally small to moderate, but homogeneous, pattern of deficits among 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). Of 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 OF, 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 among 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 to 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: (1) were younger, (2) were male, (3) had more severe OCD symptoms, and (4) were 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 OFC functioning, both known to be involved in the neurobiology of this disorder. Review of the literature[30] concerning olfactory

TABLE VII.12 Section evidence summary: Related to neurodegenerative disease

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Alzheimer disease	Waldton[595]	1974	4	Case-control	66 AD (all female) 50 HCs (all female)	Number of correct identifications of 6 odors for each of 5 test periods over 3-year period	Number of correct responses markedly depressed in AD, with performance declining over time
	Serby et al[596]	1985	4	Case-control	11 AD 20 HCs	10-odor 2-alternative forced-choice ID test presented twice Analogous tactile test	Patients with AD performed more poorly than HCs Only those who performed well on tactile test included to rule out dementia-related test-taking difficulties
	Peabody and Tinklenberg[597]	1985	4	Case-control	18 AD 26 HCs	5-odor ID task with 4 alternative choices	8 patients with AD and 1 HC had difficulty identifying odors when presented with written response alternatives
	Knupfer and Spiegel[598]	1986	4	Case-control	17 AD 18 VD 19 HC	Multiple tasks, including odor naming, recognition, forced-choice ID, 3 thresholds	For all measures, AD < VD < HCs (P<0.001 for all)
	Warner et al[599]	1986	4	Case-control	17 early-stage AD 17 HCs	UPSIT®	Patients with AD performed worse than HCs on 38 of the 40 test items Patients with AD seemed to have more difficulty in last 20 items of test
	Doty et al[600]	1987	4	Case-control	25 mild AD 25 HCs	UPSIT® PEA threshold Picture ID test (for screening out extreme dementia)	AD < HCs on both odor ID and threshold; data from only those who performed well on the picture test were included in the study
	Koss et al[601]	1987	4	Case-control	10 mild AD 8 HCs	UPSIT® Pyridine threshold	7 AD had ID deficits; only 3 had threshold deficits
	Moberg et al[602]	1987	4	Case-control	42 early AD 38 Huntington disease 42 HCs	OM Verbal and visual recognition	Olfactory memory impaired in AD and Huntington disease relative to controls Greater deficit in odor recognition than other recognition tasks
	Rezek[603]	1987	4	Case-control	18 AD 26 HCs	ID of 5 odorants Thresholds to pentanol and cinnamon oil	AD-related deficits on all measures Better ID performance with response alternatives

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Kesslak et al[604]	1988	4	Case-control	18 AD 14 PD 14 MS 18 HCs	UPSIT® Match-to-sample task using uncommon odors	Significant loss on both tests in AD and PD, but not in MS Severe impairment on match-to-sample test PD test scores lower than all other groups
	Koss et al[605]	1988	4	Case-control	10 mild AD 10 HCs	UPSIT® Pyridine threshold Cognitive tests FDG PET metabolism	AD identified fewer UPSIT® items than controls No impairment noted for threshold No correlations with neuropsych tests or FDG PET metabolism in multiple cortices
	Murphy et al[606]	1990	4	Case-control	21 AD 21 HCs	Butanol threshold Cognitive tests	No left:right differences in thresholds AD had higher thresholds than HCs (less sensitive) Thresholds correlated with MMSE, DRS, and Blessed scores
	Schiffman et al[607]	1990	4	Case-control	30 AD 8 possible AD 16 dementia other than AD 12 "young healthy elderly" 12 "old healthy elderly" 13 college-aged students	Odorant bottles interspersed with blanks at suprathreshold level	AD, possible AD, and other groups with dementia performed worse than the young and old healthy elderly and the college-aged students Dementia, rather than AD per se, influenced smell function
	Buchsbaum et al[608]	1991	4	Case-control	4 AD 6 HCs	30-trial odor match-to-sample test Odor threshold test	AD < HCs on all tests Decreased FDG PET metabolism in anterior MTC
	Doty et al[609]	1991	4	Case-control	24 early AD 24 early PD 24 patients with Parkinson-Dementia Complex of Guam	UPSIT® Picture Identification Test	When controlling for age and other factors, the degree of OD was indistinguishable between AD, PD, and patients with Parkinson-Dementia Complex of Guam
	Kesslak et al[610]	1991	4	Case-control	8 AD 7 HCs	UPSIT® Odor matching Cognitive tests MRI	AD < HCs on UPSIT® Atrophy of hippocampal, entorhinal cortex, and hippocampal and entorhinal cortex volumes correlated with olfactory test scores

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Serby et al[611]	1991	4	Case-control	55 AD 57 HCs	UPSIT® Geraniol threshold	AD < HCs on all tests Staging of AD suggests odor ID occurs earlier than threshold deficits, which occur in more advanced stages
	Perl et al[612]	1992	4	Case-control	20 AD 20 HCs	Facial muscle reactions	Odors induce less intense orofacial responses in AD, which are longer lasting
	Solomon[613]	1994	4	Case-control	10 AD	PST	9 of 10 impaired; 2 anosmic; no controls
	Morgan et al[614]	1995	4	Case-control	18 AD 18 HCs	UPSIT® SDOIT B-threshold	AD-related deficits on all measures relative to controls
	Nordin et al[615]	1995	4	Case-control	80 AD 80 normal elderly 80 sinusitis	B-threshold	Threshold: AD = sinusitis < normal elderly; normal elderly less aware of smell loss than sinusitis patients
	Nordin and Murphy[616]	1996	4	Case-control	16 questionable AD 16 HCs	OM c Multiple cognitive tests	AD < HCs on all olfactory tests
	Lehrner et al[617]	1997	4	Case-control	22 AD 21 PD 19 HCs	B-threshold 20-odor ID test Odor recognition test (15-minute interval)	Both AD and PD exhibited deficits on ID and threshold tests; only AD exhibited poorer OM
	Moberg et al[618]	1997	4	Case-control	20 AD 16 SCZ 20 HC	UPSIT®	Both AD and SCZ patients had lower scores than HCs; same loss in AD and SCZ when cognition was matched
	Nordin et al[619]	1997	4	Case-control	18 AD 16 HCs	Pyridine threshold MMSE	6 of AD, but no controls, anosmic to pyridine; the other AD patients had elevated thresholds Larger annual progression in MMSE scores for anosmic than hyposmic patients
	Ahlskog[620]	1998	4	Case-control	11 pure dementia 31 parkinsonism-dementia complex 9 ALS 9 pure parkinsonism 53 Chamorro HCs 25 North American HCs	UPSIT®	Lower UPSIT® scores in dementia and the other 3 syndromes of Guamanian neurodegenerative disease The decrement in Guamanian ALS contrasts with idiopathic ALS for which smell loss is reported to be minimal

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Bacon et al[621]	1998	4	Case-control	8 AD converters 62 stable HCs	B-threshold	Threshold changed in year before AD conversion. MCI carriers of ApoE ε4 had poorer thresholds than noncarriers
	Hawkes and Shephard[622]	1998	4	Case-control	8 AD 156 HCs	UPSIT® OERP	UPSIT® abnormal in all 8 AD patients; OERP normal in the 4 patients that could be tested
	Solomon[623]	1998	4	Case-control	20 AD 20 MD	PST	AD was differentiated from depression 1 or 0 correct on the 3-item test discriminated with a hit rate of 90% (80% sensitivity; 100% specificity)
	Bacon-Moore et al[624]	1999	4	Case-control	40 AD 40 matched HCs	B-threshold Odor ID Odor fluency	AD performed worse on odor threshold; OM, as reflected by ability to generate odor names to cued odors or names of odors, lower in AD
	Larsson[625]	1999	4	Case-control	11 AD 11 HCs	B-threshold ID: free ID, verbal cues, visual cues, odor matching	No significant B-threshold differences; AD performed more poorly on odor ID composite, with poorer performance on odor matching test
	Niccoli-Waller et al[626]	1999	4	Case-control with longitudinal prospective arm	32 AD 32 HCs	B-threshold 10-odor longitudinal familiarity memory test	Poorer threshold scores in AD Remote memory for odors, measured by familiarity test 1 year later, more impaired in AD than remote memory for some visual stimuli
	McCaffrey et al[627]	2000	4	Case-control	20 AD 20 MD	PST	Test discriminated between AD and depression with a hit rate of 97.5% (95% sensitivity; 100% specificity)
	Gray et al[628]	2001	4	Case-control	13 AD 13 VD 13 HCs	UPSIT®	AD scores = VD scores; all lower than those of HCs UPSIT® correlated 0.68 with the degree of cognitive impairment measured by CAMCOG
	Kareken et al[629]	2001	4	Case-control and PET imaging	7 AD 8 HCs	UPSIT® PEA threshold PET imaging	UPSIT® but not PEA threshold impaired in AD Odors activated left and right piriform areas and right anterior ventral temporal cortex

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
							AD had less activation in right piriform and anterior ventral temporal cortex but not in the left piriform area Right piriform activation correlated with UPSIT® scores
	McShane[630]	2001	4	Case-control	92 AD 94 HCs	Perception of 1 concentration of lavender water Postmortem measures of LB and other AD pathology	Patients with LB in cingulate gyrus more likely to be anosmic than HCs (41% vs 6%) Non-LB AD not more likely to be anosmic than HCs CAMCOG no worse in anosmics than in nonanosmics Study limited by questionable olfactory test
	Royet et al[631]	2001	4	Case-control	15 AD 15 older HCs 15 younger HCs	Odor ID, ratings of intensity, hedonics familiarity, edibility	Intensity scores were lower in older controls and AD patients than in the younger controls and familiarity and ID scores were lower in AD patients than in older controls and younger control No differences between groups for pleasantness and edibility judgements
	Chan et al[632]	2002	4	Case-control	12 AD 12 HCs	SDOIT AST	AD performed more poorly on both olfactory tests, identifying fewer odors and having higher AST threshold than age- and education-matched HCs
	Duff et al[633]	2002	4	Case-control	20 AD 20 VD 20 MD	PST	AD scores were lower than VD or MD Test discriminated with 95% classification accuracy (100% sensitivity; 92.5% specificity)
	Lange et al[634]	2002	4	Case-control	48 AD 15 PD 41 mixed diagnoses 73 HCs	UPSIT®	Rasch scaling determined that decline of UPSIT® in AD equivalent to that experienced by HCs over the course of 30 years UPSIT® reliability was high (KR-20 = 0.93)

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Morgan and Murphy[635]	2002	4	Case-control	12 AD 12 HCs OERP	UPSIT® B-threshold SDOIT	Tests differentiated between AD and HCs Combining sensory and OERP P3 latency produced 100% correct classification
	Wang et al[636]	2002	4	Case-control	28 MCI 30 age-matched HCs	B-SIT	B-SIT scores lower in MCI than in HCs The scores correlated positively with CAMCOG-Chinese version, but not with age, sex, or years of education ApoE ε4 allele frequency was higher in MCI than in HCs MCI allele carriers identified fewer odors
	Murphy et al[637]	2003	4	Case-control and MRI imaging correlations	12 AD 22 HCs	SDOIT B-threshold	AD exhibited poorer ID and threshold performance Strong correlation (r = 0.85) between SDOIT and left hippocampal volume in AD Strong correlations in HCs between olfactory measures and mesial temporal lobe volumes
	Getchell et al[638]	2003	4	Case-control	18 AD 6 HCs	AST	AST thresholds elevated relative to HCs
	Peters et al[639]	2003	4	Case-control	14 AD 8 MCI 8 HCs	SS-TDI OERP	TDI score indicated 12 of AD and 7 of MCI were hyposmic All HCs were normosmic OERP absent in 4 of MCI and in 7 of AD OERP present in a number of hyposmic AD and MCI
	Westervelt et al[640]	2003	4	Case-control	9 AD 9 LBD	B-SIT	Both AD and LBD exhibited dysfunction, although performance was lower in LBD than in AD (64% correct in AD and 32% correct in LBD)
	Gilbert et al[641]	2004	4	Case-control	12 AD 12 LBD 12 HCs	OM B-threshold	LBD performed worse than AD AD performed worse than HCs

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Gilbert et al[642]	2004	4	Case-control	38 pathologically confirmed AD 38 probable AD 38 elderly HCs	B-threshold RMT	AD performed more poorly on threshold task Hit rate on memory test was same among groups, but false-positive rate was elevated for the AD as well as ApoE ε4+ without dementia
	Suzuki et al[643]	2004	4	Case-control	85 AD 30 HCs	B-SIT Picture-based ID test	AD compromised on both olfactory tests Picture test discriminated better between the 2 groups Within AD, higher correlations between Picture-based ID test scores and MMSE scores were present for ApoE ε4 allele carriers than noncarriers
	Eibenstein et al[644]	2005	4	Case-control	29 aMCI 20 HCs	SS-ID (16 odors)	aMCI showed impairment in smell function relative to controls
	Sparks et al[645]	2005	4	Retrospect case-control	9 AD 21 MCI 16 high-function HCs 24 high-function HCs	UPSIT®	AD had lower odor ID scores than either the MCI or the 2 HC groups, which did not differ from one another
	Tabert et al[646]	2005	4	Case-control	100 AD 147 MCI 63 HCs	UPSIT® B-SIT 10-item ID test	For all tests, AD scores < MCI < HCs 10 items from UPSIT® found to be optimal in making these differentiations
	Motomura and Tomota[647]	2006	4	Case-control	12 AD 12 VD 30 HCs	B-SIT	Scores were low in AD compared with VD and HCs, which did not differ from one another
	Kjelvik et al[648]	2007	4	Case-control	39 AD 52 HCs	B-SIT	Olfactory testing distinguished the 2 groups with high sensitivity and specificity AD-associated memory impairment was not related to the test scores

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Luzzi et al[649]	2007	4	Case-control	14 AD 11 FTD 8 patients with semantic dementia 7 CBD 20 HCs	Odor naming, discrimination, odor-picture matching, picture naming, word-picture matching tests	Only AD performed worse than HCs on odor discrimination All dementia groups performed worse than HCs on odor naming and odor-picture matching Only patients with semantic dementia performed more poorly than HCs on picture naming and word-picture matching tests (which involved no odors)
	Pentzek et al[650]	2007	4	Case-control	30 AD 20 MD 31 HCs	SS-ID (16 odors)	AD had significantly lower test scores than HCs The SS-ID scores of the depressed patients were equivalent to those of the HCs
	Sundermann et al[651]	2007	4	Case-control	19 ApoE ε4 AD 19 no ApoE ε4 19 ApoE ε4 HCs 19 no APoE ε4 HCs	B-threshold Recognition Memory Test	B-thresholds higher (less sensitivity) in AD ApoE ε4–positive HC men, but not their female counterparts, performed more poorly on OM test In AD, ApoE ε4–negative women performed better than ApoE ε4–positive women
	Wilson et al[652]	2007	4	Case-control	177 incident MCI 412 HCs	B-SIT	MCI performed poorly on olfactory test vs HCs Among older persons without manifest cognitive impairment, difficulty in identifying odors predicts subsequent development of MCI
	Devanand et al[653]	2008	3	Cohort	148 MCI tested at 6-month intervals for conversion to AD	UPSIT®	At 3 years, 33 of 126 converted; UPSIT® + 4 other measures optimized detection of converters
	Djordjevic et al[654]	2008	4	Case-control	27 AD 51 MCI 33 HCs	UPSIT® PEA threshold 32-trial same/different discrimination test	For all tests, AD < MCI < HCs Authors concluded that ID and threshold deficits occur early in AD, before clinical symptoms are fully developed, and decline further as disease progresses

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	McLaughlin and Westervelt[655]	2008	4	Case-control	14 AD 14 FTD 14 HCs	B-SIT	Both AD and FTD had lower scores than the HCs and did not differ significantly from one another
	Westervelt et al[656]	2008	4	Case-control	44 AD 83 MCI 21 HCs	B-SIT	AD had lower scores than MCI Both had lower scores than HCs Subtypes of MCI did not differ Only modest difference between MCI and HCs
	Jungwirth et al[657]	2009	4	Case-control	88 AD 384 HCs	3-PST	Lower scores in AD than in HCs
	Laakso et al[658]	2009	4	Case-control	72 MCI 486 HCs	Spontaneous and cued odor ID and delayed recall BNT	MCI scored below HCs on both odor and BNT, but impairment odor less impaired than BNT
	Lehrner et al[659]	2009	4	Case-control	19 MCI 11 single domain aMCI 19 multiple domain aMCI 21 single domain naMCI 13 multiple domain naMCI 40 HCs	UPSIT®	Odor ID scores differed between aMCI multiple domain patients and the HCs Other differences not significant Moderate correlations between UPSIT® scores and age, subjective smell loss, and MMSE scores
	Wilson et al[660]	2009	3	Cohort	471 cognitively normal older people at baseline	B-SIT Cognitive measures Autopsy of pathologies	Annual clinical evaluations were made and brains were autopsied at death in 34 B-SIT scores were associated with more cognitive impairment and with higher level of AD pathology, even after controlling for ApoE ε4 and premortem level of episodic memory function
	Devanand et al[661]	2010	4	Case-control	170 aMCI 120 naMCI 802 no MCI	UPSIT® Cognitive measures	Test scores: no MCI > naMCI > aMCI UPSIT® scores correlated with SRT immediate recall, delayed recall, category fluency, and BNT

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Devanand et al[662]	2010	3	Cohort	31 MCI that converted to AD MCI 96 nonconverters 59 HCs	UPSIT®	At baseline, MCI converters to AD had lower UPSIT® scores than nonconverters whose scores did not differ from HCs
	Williams et al[663]	2009	4	Case-control	27 mild AD 21 mild DLB 21 mild MCI 47 HCs	SS-ID (16 odors)	SS-ID scores were lower in MCI, mild AD, and mild DLB than HCs Using logistic regression, the smell ID score predicted diagnosis of DLB rather than mild AD independent of age, sex, and cognitive function
	Forster et al[664]	2010	4	Case-control	6 incipient AD 18 mild AD 28 matched HCs	SS-TDI FDG uptake	AD exhibited reduced threshold, discrimination, and ID scores ID scores correlated with FTG clusters in right superior parietal lobule, fusiform gyrus, inferior frontal gyrus, and precuneus Discrimination scores correlated with a single cluster in the left postcentral cortex Threshold scores correlated with right thalamus and cerebellum clusters
	Fusetti et al[665]	2010	3	Cohort	30 AD 29 aMCI	SS-TDI	At 18-month follow-up, 9 (31%) converted to AD and had lower test scores than nonconverters
	Li et al[666]	2010	4	Case-control	10 AD 10 matched HCs	UPSIT® SS-T (PEA) Suprathreshold ratings of odor affective valence, intensity, familiarity fMRI cross-adaptation paradigm	UPSIT®, but not PEA threshold, poorer in AD Odor quality ratings disrupted in AD, a phenomenon suggested to be caused by functional disruption of circuits within the posterior piriform cortex

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Razani et al[667]	2010	4	Case-control	12 AD 12 HCs	Similarity judgments of odors and colors subjected to multidimensional scaling	Multidimensional scaling spatial odor maps of AD exhibited disorganized groupings relative to those of HCs This was not true of color maps Label matching and attribute sorting deficits suggested semantic OM is compromised
	Steinbach et al[668]	2010	4	Case-control	30 AD 29 MCI 29 HCs	SS-TDI	AD scores < MCI scores < HCs on all smell test components save no T difference between AD and MCI AD had lower scores than MCI ID, discrimination, and threshold all affected
	Wang et al[669]	2010	4	Case-control fMRI	12 AD 13 HCs	UPSIT®	AD had less function than HCs BOLD signals correlated with UPSIT® in the primary olfactory cortex, hippocampus, and insula
	Bahar-Fuchs et al[670]	2011	4	Case-control	25 AD 25 MCI 22 HCs	6 items from UPSIT® Unirhinal testing Subjective perception	AD and aMCI performed more poorly than HCs AD and aMCI did not differ No left/right nostril differences Majority of patients fell below normal Patients generally unaware of OD
	Hidalgo et al[671]	2011	4	Case-control	11 AD 4 VD 15 age- and sex-matched HCs	Just noticeable difference tool using standard and different butanol concentrations	Combined AD and VD group had larger just noticeable differences than HCs AD only had largest difference from HCs
	Jimbo et al[672]	2011	4	Case-control	100 AD 17 age-matched HCs	OSIT-J	AD associated with lower test scores than HCs Severe AD had lower scores than mild AD
	Makowska et al[673]	2011	4	Case-control	30 AD 30 young HCs 30 elderly HCs	PST	AD exhibited decline in test scores relative to other groups Elderly HCs exhibited lower scores than young HCs Cognitive measures correlated with test scores in the AD and elderly HCs

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Schofield et al[674]	2012	3	Cohort	14 probable AD 13 MCI, no dementia 29 HCs	UPSIT®	Anticholinergics exaggerate cognitive decline in AD, presumably reflecting less cholinergic capacity Authors hypothesized that intranasal atropine should decrease UPSIT® scores more in cognitively at-risk patients and, in turn, impact episodic memory The decrement from the "anticholinergic challenge" was 31% in HCs, 92% in MCI with no dementia, and 86% in AD They suggest this test might provide an inexpensive screen for preclinical AD
	Sohrabi et al[675]	2012	3	Cohort	308 participants aged 46 to 86 years	SS-TDI Cognitive measure decline	At 3-year follow-up, lower test scores present in CD than in non-CD SS-D but not SS-ID significantly predicted CD
	Conti et al[676]	2013	3	Case-control and cohort	67 MCI 46 HCs	UPSIT® PEA threshold OM test	At baseline, 40% of MCI had normal ID scores; all HCs were normal The olfactory-impaired MCI had higher PEA thresholds than the olfactory normal MCI and controls, but OM was the same 47% of olfactory-impaired MCI and 11% of non-OI MCI patients converted to AD over a 2-year period
	Seligman et al[677]	2013	4	Case-control	172 AD 112 MCI 132 HCs	SS-ID	AD and MCI scores lower than HCs, with AD being lower than MCI AD had more apathy than MCI and HCs SS-ID correlated negative with apathy scores
	Stamps et al[678]	2013	4	Case-control	18 AD 29 HCs	PBT	Authors reported that all 18 AD had poorer PBT performance on the left than the right side of the nose, and that the performance on the right side of the nose was the same as HCs

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Velayudhan et al[679]	2013	3	Case-control and cohort	57 mild to moderate AD 24 elderly	UPSIT® baseline and 3-month retest scores	AD had lower baseline scores than HCs MMSE scores related to baseline UPSIT® scores but not to change over time
	Doty et al[680]	2014	4	Case-control	20 AD tested on left and right with UPSIT®; 15 with PBT	UPSIT® PBT	No AD-related systematic left/right differences in test scores, in contradiction to the study by Stamps et al[678]
	Kjelvik et al[681]	2014	4	Case-control	6 early AD 12 aMCI 30 HCs	B-SIT SS-ID	AD and aMCI groups performed worse than HCs on both tests Hippocampal volume down in those with most OD
	Margliano et al[682]	2014	3	Cohort	18 aMCI cohort followed up at 12 months	SS-TDI at baseline MRI volume of hippocampus	At follow-up, 5 (28%) converted to AD Both SS-TDI score and hippocampal volume loss showed same sensitivity to conversion (92.3%), but SS-TDI had a higher sensitivity (75% vs 60%)
	Stanciu[683]	2014	3	Cohort	1529 community members with normal cognition at baseline followed over a 10-year period	SOIT SS-T Self-ratings of smell dysfunction	159 (10%) converted to dementia Conversion predicted by demographic variables, MMSE, and olfactory assessments, including self-reports and olfactory test scores, with the olfactory measures being additive
	Devanand et al[684]	2015	3	Cohort	757 community members without dementia followed up at 2 years and 4 years	UPSIT®	Lower baseline UPSIT® scores associated with transition to AD dementia 101 (13%) participants transitioned to AD dementia
	Hori et al[685]	2015	4	Case-control	12 patients with AD aged 62 to 85 years 40 HCs aged 20 to 43 years 35 HCs aged 45 to 69 years 38 HCs aged 70 to 89 years	OSIT-J Odor judgement test (eg, good/bad; safe/harmful)	AD had lower scores in both olfactory tests than age-matched controls Scores on both tests were lower in the older HCs than in the younger age groups Age correlated with test scores in the non-AD groups

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Servello et al[686]	2015	4	Case-control	25 mild AD 25 aMCI 28 HCs	SS-TDI	AD scores < MCI < HCs Same pattern for subtests No correlations between test scores and OBV
	Velayudhan et al[687]	2015	4	Case-control	54 mild to moderate AD 40 matched HCs	Subset of UPSIT® items that best differentiated early AD from HCs	12 UPSIT® items identified using machine learning that best differentiated AD from HCs
	Hagemeier et al[688]	2016	4	Case-control	42 AD 19 aMCI 19 HCs	UPSIT® Cognitive measures	AD and aMCI had lower UPSIT® scores than HCs ApoE ε4 allele frequency higher in AD and aMCI, and inversely associated with UPSIT® scores In aMCI, olfactory test scores correlated with neocortical volumes, hippocampal volumes, and amygdala volumes In AD, olfactory performance was correlated with deep gray matter, cortical, and central atrophy
	Roberts et al[689]	2016	3	Cohort	1430 cognitively normal older patients at baseline	B-SIT (version A)	Over 3.5 years of follow-up, 250 incident cases of MCI (17.5%). Decrease in B-SIT scores associated with increased risk of aMCI but not naMCI. Scores also predicted progression from aMCI to AD dementia, with significant dose-response with worsening B-SIT quartiles
	Christensen et al[690]	2017	4	Case-control	20 AD and 20 HCs (nonblinded study) 24 AD and 26 HCs (blinded study)	PST (2-and 3-item versions)	None of the AD had zero errors. In blinded study, diagnosis of probably AD was 48%, MCI 24%, VD 8%, alcohol-induced impairment 12%, depression 4% and PD and LBD 2%
	Devanand et al[691]	2017	3	Cohort	37 MCI	UPSIT® Changes in SRT total immediate recall and ADAS-Cog total score from baseline to 26 and 52 weeks	Intranasal anticholinergic challenge–induced odor ID decline, which reflects greater cholinergic deficiency, was associated with subsequent better cognitive efficacy from 8-week treatment with a cholinesterase inhibitor

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Lafaille-Magnan et al[692]	2017	3	Cross-sectional	274 healthy older persons with parental or multiple-sibling history of AD	UPSIT® Cognitive measures CSF levels of T-tau, P-tau, and ratios with Aβ1-42	Reduced smell test scores associated with lower cognitive scores and older age, as well as increased ratios of CSF T-tau and P-tau to Aβ1-42 Suggests OI reflects degree of preclinical AD pathology
	Passler et al[693]	2017	4	Case-control	7 AD 22 NPH 14 HCs	UPSIT®	AD scores lower than NPH scores NPH scores below HC scores, although still within normal limits Suggests that olfactory testing may be useful in differentiating AD from NPH
	Quarmley et al[694]	2017	4	Case-control	262 AD 150 aMCI 24 naMCI 292 HCs	SS-ID (16 odors) MoCA	Better SS-ID scores in HCs MCI outperformed AD Combining olfactory and cognitive measures improved diagnosis of AD and MCI
	Reijs [695]	2017	3	Case-control and cohort	42 AD 45 MCI 26 non-AD dementia 40 HCs	B-SIT Cognitive measures CSF Aβ42 CSF t-tau ApoE genotype	At baseline, lower B-SIT scores correlated with increased CSF t-tau and were lower than HCs in all diagnostic groups Lower scores predicted MMSE decline in total group, and word list learning and delayed recall in ApoE ε4 carriers and those with abnormal Aβ42 Concluded OD may reflect neuronal injury rather than amyloid pathology
	Risacher et al[696]	2017	4	Case-control	10 SCD 5 MCI 19 HCs	Association of UPSIT® scores with PET measures of tau and amyloid burden	Lower UPSIT® scores associated with increased temporal and parietal tau, but not amyloid, burden
	Roalf et al[697]	2017	1	Meta-analysis of case-control and cohort studies	1993 MCI 2861 HCs	Psychophysical examinations (eg, UPSIT® and SS-TDI)	Quantitative meta-analysis indicates robust olfactory deficits in patients with MCI Olfactory ID test may be useful in early screening for cognitive impairment and dementia

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Woodword et al[698]	2017	4	Case-control	262 AD 110 aMCI 194 HCs	UPSIT®	High sensitivity of UPSIT® for identifying AD and aMCI 34% of aMCI with impaired olfaction and 17.3% with intact olfaction converted to AD
	Kreisl et al[699]	2018	4	Case-control	46 aMCI 23 HCs	UPSIT® PIB Amyloid-β PET measure	Those with high UPSIT® scores were less likely to have cerebral amyloidosis or memory decline
	Palta et al[700]	2018	2	Cross-sectional	5021 community residents aged 45 to 64 years	SS-ID (12 odors) Cognitive tests	1092 diagnosed with MCI Those with OI had lower memory, language, executive function, and general cognitive performance OI was lower in MCI than in non-MCI
	Park et al[701]	2018	4	Case-control	20 mild AD 50 aMCI 28 naMCI 27 SMI	B-SIT Cognitive tests	OI more severe in AD and aMCI compared with naMCI and SMI groups Olfactory ID ability was positively related to MMSE, verbal and nonverbal memory, and frontal executive function
	Woodward et al[702]	2018	3	Cohort and case-control	415 AD 192 aMCI 234 HCs Longitudinal prediction of AD from aMCI and ID of optimal UPSIT® items	UPSIT®	Identified subsets of UPSIT® items that individually associated with AD and age useful for assessing risks for AD
	Yu et al[703]	2018	4	Case-control	60 AD 37 MCI 30 HCs HRS Self-reported loss Cognitive measures	SS-TDI	Respective frequency of dysfunction in HC, MCI, and AD groups: SS – 3.3%, 13.5%, 65%; self-report – 10.3%, 13.5%, 18.3%; HRS – 6.7%, 24.3%, 48.3% AD with OD compared with AD without OD exhibited declines in global cognition and memory, visuospatial ability, and attention

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Lian et al[704]	2019	4	Case-control	30 AD with OD 30 AD without OD	SS-TDI Cognitive meaures MRI-determined structural volumes	Frequency of OD was 50% defined by SS-TDI OD associated with a reduction in cortical thickness, more cognitive dysfunction, and lower hippocampal and amygdala volumes, as well as more compromised daily-living activities ID and discrimination more strongly associated than threshold SS measures with structural volumes
	Lu et al[705]	2019	4	Case-control	12 AD 19 MCI 31 matched HCs	Cognitive tests UPSIT® fMRI of multiple brain structures related to CNS neural olfactory network	UPSIT® scores lowest in AD, next lowest in MCI, and normal in HCs Scores were positively correlated with cognitive test scores among all patients fMRI olfactory network exhibited diminished activation in both MCI and AD, with more decrement in AD
	Velayudhan et al[706]	2019	4	Case-control	19 early-onset AD 17 MCI 21 HCs	UPSIT® Cognitive measures	Smell loss > in early onset AD compared with MCI and HCs In AD, UPSIT® scores correlated >0.49 with attention, executive function, and praxis measures
	Yoshii et al[707]	2019	4	Case-control	55 AD 27 MCI	OSIT-J cognitive tests MRI	Test scores lower in AD than in MCI and correlated with ADAS-Jcog scores OD associated with atrophy of the medial temporal lobe, including hippocampal and parahippocampal regions
	Yahiaoui-Doktor et al[708]	2019	3	Cohort	6783 population sampled	SS-ID (12 odors) CERAD cognitive battery	Based on different CERAD components, 6% to 11% of the sample were cognitively impaired Better olfactory performance was associated with better cognitive performance on all measures, although ability of the smell test to discriminate between those with and without cognitive impairment was limited

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Yu et al[709]	2019	4	Case-control	31 MCI 9 HCs	UPSIT® MRI brain structure volumes	Hippocampal volumes lower in MCI than in HCs Correlation between UPSIT® scores and volumes
	Wu et al[710]	2019	4	Case-control	37 AD 27 MCI 30 HCs	CSIT MRI brain structure volumes	AD and MCI scores lower than HC scores Strong relationships found between CSIT scores and volumes of the amygdala, and the left precentral and inferior frontal gyri
	Baek et al[711]	2020	4	Case-control	55 hyposmic 72 nonhyposmic	B-SIT Cognitive tests MRI brain structure volumes	ApoE ε4 allele more common in hyposmics who have lower MMSE, memory, language, visuospatial, and executive function scores No difference between groups in regional Aβ and tau burden Hyposmic group had smaller entorhinal cortex volumes Aβ-positive hyposmics had reduced volumes of global cortex, superior and middle temporal, and entorhinal cortices, amygdala, and hippocampus
	Beach et al[712]	2020	4	Case-control	66 ADD 29 ADD/DLB 39 ADD/LBD not meeting criteria for DLB 21 PDD+AD 27 PDD-AD 84 HCs	UPSIT®	Patients with neuropathologically confirmed ADD + DLB have worse olfaction than those with ADD alone
	Devanand et al[713]	2020	3	Cohort	1037 community-living older adults without dementia; 749 followed up within 4-year period	B-SIT Cognitive tests (eg, BOMCT)	B-SIT and BOMCT each predicted dementia (11% converted). Only 3.4% converted to dementia if they had intact olfaction and a good score on the BOMCT

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Devanand et al[714]	2020	3	Cohort	100 MCI	UPSIT® Changes in ADAS-Cog total score and, SRT total immediate recall from baseline to 52 weeks	Although intranasal anticholinergic challenge–induced initial odor ID decline, which reflects greater cholinergic deficiency, the decline was not associated with better cognitive efficacy from a 52-week treatment with a cholinesterase inhibitor This is a failure to replicate the findings of an earlier smaller study[691]
	Doorduijn et al[715]	2020	4	Case-control	30 AD 22 MCI 40 HCs	SS-TDI Cognitive tests of 5 domains	AD and MCI showed deficits on ID and discrimination but not threshold Poorer memory associated with poorer discrimination and ID but not threshold No correlations with CSF levels of tau, P-tau, or Aβ1-42
	Olofsson et al[716]	2020	3	Cohort	1637 patients aged 60 to 96 years	Sniffin' test of OM	Lower odor ID performance was predictive of cognitive decline, an effect most pronounced among ApoE ε4 carriers
	Zhao et al[717]	2020	3	Cohort	88 AD at baseline 80 HCs at baseline 87 MCI with 2- and 3-year follow-up	SS-ID (16 odors)	Lower SS-ID scores and higher neuronal-derived exosome Aβ1-42 levels in AD and MCI at baseline SS-ID predicted conversion to AD SS-ID + neuronal-derived exosome Aβ1-42 levels provided stronger prediction
	Dong Y[718]	2021	3	Cohort	4514 rural Chinese patients aged >64 years	SS-ID (16 odors)	142 of the sample diagnosed with dementia, one of several factors correlated with smell loss (others included age, smoking behavior, education, body weight, head injury, and nasal sinus disease) Prevalence of OI was 67.6%
	Jobin et al[719]	2021	1	Meta-analysis of case-control studies	264 SCD 334 HCs	UPSIT®, SS-ID, B-SIT, OPID test	Quantitative meta-analysis indicates slight olfactory deficits in SCD compared with HCs

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Klein et al[720]	2021	2	Cross-sectional	54 normal and cognitively impaired PET imaging of tau in 41 and 18 kDa translocator protein in 53	UPSIT®	Low ID scores associated with greater tau pathology in medial temporal cortex, hippocampus, middle and inferior temporal gy, and posterior cingulate cortex
	Li et al[721]	2021	4	Case-control	24 AD 24 MCI 33 HCs	AROMA test SS-ID (12 odors)	MCI/AD scored less than HCs AROMA test superior to SS-ID in discrimination MCI could be differentiated from AD SS-D differentiates HCs from AD and MCI
	Motter et al[722]	2021	3	Cohort	100 MCI	UPSIT® Changes in ADAS-Cog total score and SRT total immediate recall from baseline to 52 weeks	Although intranasal anticholinergic challenge–induced initial odor ID decline, which reflects greater cholinergic deficiency, the decline was not associated with better cognitive efficacy from a 52-week treatment with a cholinesterase inhibitor This is a failure to replicate the findings of an earlier smaller study[691]
	Sundermann et al[723]	2021	4	Case-control	31 high aMCI+HAND 26 low aMCI+HAND 4 high aMCI no HAND 20 low aMCI no HAND	UPSIT®	Test scores lower in the high vs low aMCI groups independent of HAND status
	Wang et al[724]	2021	4	Case-control	52 AD 129 MCI 84 SCD 35 HCs	SS-ID (16 odors) Cognitive tests	Scores were poorest for AD followed by MCI, SCD, and HCs In AD and MCI, SS-ID correlated with global cognition Among the different cognitive domains, SS-ID correlated most strongly with memory

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Amyotrophic lateral sclerosis (motor neuron disease)	Elian[725]	1991	4	Case-control	14 ALS 14 matched HCs	UPSIT®	Marked decrease in test scores of ALS
	Sajjadian et al[726]	1994	4	Case-control	37 ALS 37 matched HCs	UPSIT®	75.7% of ALS had UPSIT® scores below that of their matched controls 11% of ALS were anosmic Positive correlations noted between UPSIT® scores and measures of peripheral nerve conductance
	Hawkes and Shephard[727]	1998	4	Case-control	58 ALS 154 HCs	UPSIT®	16% of ALS group had abnormal UPSIT® scores and 10% delayed OERP
	Lang et al[728]	2011	4	Case-control	26 ALS 26 HCs	SS-ID (12 odors)	No effect of ALS on unilaterally administered test scores; however, added left and right nose side scores to double sample size, which is statistically questionable
	Takida et al[729]	2015	4	Case-control	18 ALS 18 HCs	OSID-J Histochemical studies of brain TAR DNA-binding protein 43 , tau, and α-synuclein in ALS	ALS scored lower than HCs Test scores paralleled the cognitive decline TAR DNA-binding protein 43, tau, and α-synuclein accumulations appeared to be independent, with TDP-43 positive inclusions more abundant in the hippocampus and less in the OB, in contrast to accentuation of α- synuclein in the OB
	Pilotto et al[730]	2016	4	Case-control	11 ALS with normal cognition 17 ALS with FTD Spectrum 30 HCs	SS-ID (12 odors) + parallel picture response version	ALS with normal cognition exhibited normal performances ALS with FTD was impaired on both olfactory and cognitive tasks relative to HCs
	Viguera et al[731]	2018	4	Case-control	78 ALS 69 HCs	UPSIT®	UPSIT® scores lower in ALS than in controls, with twice the rate of OD

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Matsuda et al[732]	2021	4	Case-control	30 ALS 53 matched HCs	OSIT-J MRI voxel-based morphometr Cognitive tests	OSIT-J score significantly lower in ALS than in HCs Test scores correlated with age and a number of cognitive measures, including frontal assessment battery, but not education or disease type OSIT-J scores were correlated with atrophic changes of left orbital cortex consisting of gyrus rectus and medial orbital gyrus and right hippocampus in ALS
Multiple sclerosis	Ansari[733]	1976	4	Case-control	24 MS 24 HCs	Amyl acetate and nitrobenzene recognition thresholds	No differences in thresholds between MS and HCs
	Pinching [734]	1977	4	Cross-sectional	22 MS	Yes/no detection + quality descriptions	45% exhibited anosmia or microsmia
	Doty et al[735]	1984	2	Case-control	31 MS 1215 HCs	UPSIT®	7 of 31 MS (31%) exhibited microsmia Test scores correlated with disease duration after correcting for age
	Kesslak et al[604]	1988	4	Case-control	14 MS 14 HCs	UPSIT® Match-to-sample discrimination test	No difference in test scores, although more women in the HCs and MS younger than HCs
	Doty et al[736]	1997	2	Cross-sectional	26 MS	UPSIT® MRI lesion counts	Strong negative relationship found between UPSIT® scores and the number of demyelinated plaques within the inferior frontal and temporal lobes
	Hawkes and Shephard[737]	1997	4	Case-control	72 MS 154 HCs	UPSIT® OERP	15% had abnormal UPSIT® scores; 23% slight delay in latency and decrease in OERP amplitude UPSIT® scores correlated significantly with measures of anxiety, depression, and severity of neurological impairment Only 2% of patients aware of smell loss until being tested

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Doty et al[738]	1999	3	Cohort	5 MS	UPSIT® MRI plaque numbers	Over an 18- to 20-month period, as plaque numbers decline in the inferior frontal and temporal lobes, OF increases, whereas plaque numbers increase in these brain regions, OF decreases
	Zivadinov et al[739]	1999	4	Case-control	40 MS 40 HCs	B-SIT Cognitive tests	12.% of MS exhibited abnormal smell function and 10% borderline function Relationship between smell loss and degree of MS impairment, as well as symptoms of anxiety and depression
	Zorzon et al[740]	2000	4	Case-control	40 MS 40 HCs	B-SIT MRI	MS scored lower than HCs Robust negative correlation between smell function and lesion load in white matter in inferior frontal and temporal lobes
	Fleiner et al[741]	2010	4	Case-control	16 MS 16 HCs	SS-TDI Taste powder test	50% of MS exhibited hyposmia 25% exhibited retronasal deficit using oral flavor powders No correlation between orthonasal and retronasal test scores
	Goektas et al[742]	2011	4	Case-control	36 MS 36 HCs	SS-TDI MRI OBV	44.4% of MS exhibited dysfunction OBVs correlated with test scores
	Lutterotti et al[743]	2011	4	Case-control	50 MS 30 HCs	SS-TDI	MS had lower scores on TDI, ID, and threshold than HCs Threshold was impaired in patients who were clinically active the year before and in those with <2 years' disease duration ID negatively correlated with disease duration
	Dahlslett et al[744]	2012	4	Case-control	30 MS 30 HCs	SS-TDI OERP	40% of MS exhibited smell loss 23.8% OERPs suggestive of hyposmia Inverse correlation between TDI and EDSS score

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Erb et al[745]	2012	4	Case-control	30 MS 30 HCs	SS-TDI DTI	TDI and ID lower in MS than in HCs Threshold and discrimination scores similar in both groups Fractional anisotropy of lesions in olfactory regions inversely correlated with ID
	Silva et al[746]	2013	4	Case-control	153 MS 165 HCs	B-SIT	11.3% more impaired than HCs (3%) Secondary progressive MS impaired more than relapsing-remitting MS primary progressive MS (respective frequencies: 68.3%, 3.3.%, and 12.5%)
	Rolet et al[747]	2013	3	Cross-sectional	50 MS	SS-TDI	40% of patients were hyposmic on threshold ID affected later and inversely related to disability level
	Erb-Eigner et al[748]	2014	4	Case-control	30 MS 12 HCs	SS-TDI DTI	Degree of ID olfactory impairment in MS correlated with the decrease in fractional anisotropy and increase in mean diffusivity in olfactory structures
	Holinski et al[749]	2014	2	Cross-sectional	20 MS	OERP MMSE	25% of patients hyposmic and exhibited higher OB lesion volumes and smaller OBVs OERP latencies correlated with volume and number of lesions OBVs negatively correlated with MMSE scores
	Caglayan et al[750]	2016	4	Case-control	30 MS 30 HCs	SS-TDI	No differences in olfactory test scores among the 3 groups No correlations between such scores and MMSE, EDSS, disease duration, history of optic neuritis, or taking immunomodulatory therapy
	Jordy et al[751]	2016	4	Case-control	100 MS 100 HCs	CCCRC olfactory test	32% of MS exhibited smell dysfunction compared with 3% of HCs MS with EDSS score >4 had 5.2 times increased risk of dysfunction

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Kandemir et al[752]	2016	4	Case-control	26 MS 20 HCs	B-SIT MRI brain structure volume measures	MS exhibited lower olfactory scores than HCs MRI volumes of amygdala were larger in MS than in HCs
	Li et al[753]	2016	3	Case-control	26 MS 26 matched HCs	T&T olfactometer MRI brain structure volume measures	Detection and recognition thresholds higher in MS than in HCs Recognition threshold correlated with EDSS score Patients with OD had smaller OBs and less gray matter in the parahippocampal gyrus, amygdala, piriform cortex, and inferior frontal gyrus
	Good et al[754]	2017	4	Case-control	73 MS 73 matched HCs	UPSIT® PEA Threshold MRI brain structure volumes	Test scores lower in MS than in HCs No significant differences between left and right sides of the nose for ID and threshold measures but scores on the 2 sides correlated with one another The percent of MS whose bilateral test scores fell below the 10th percentile of controls did not differ between the odor ID and detection threshold tests Both ID and threshold scores weakly correlated with lesion volumes in temporal and frontal lobe brain regions
	Uecker et al[755]	2017	3	Cohort	20 MS	SS-TDI OERP	Patients tested for 3 years after initial test At follow-up, 45% showed OD and 50% showed delayed OERPs Discrimination scores inversely correlated with number of relapses
	Atalar et al[756]	2018	4	Case-control	31 MS 24 HCs	CCCRC olfactory test	MS olfactory scores lower than HCs Lower scores associated with longer disease durations and more frequent attacks

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Li et al[757]	2018	4	Case-control	37 MS 37 with neuromyelitis optica	T&T thresholds	40.5% of MS and 51.5% of patients with neuromyelitis optica exhibited smell dysfunction Dysfunction associated with smaller OBs, with NMO having the smallest ones gray matter atrophy noted in MS in right parahippocampal gyrus and piriform cortex Neuromyelitis optica atrophy within the orbitofrontal cortex and right superior frontal gyrus
	Bsteh et al[758]	2019	3	Cohort	151 MS 30 HCs	SS-TDI	Discrimination and ID worsened over 3-year period Threshold impaired in patients with relapse activity within 12 months, recovered in the absence of relapse, and was associated with a 2.5-fold increased risk of relapse Deterioration of discrimination and ID was irreversible and both strongly associated with and predictive of EDSS progression
	Carotenuto et al[759]	2019	4	Case-control	55 MS 20 HCs	UPSIT® Cognitive measures	UPSIT® performance decreased in MS, with secondary-progressive and cognitively impaired MS patients showing most impairment Scores on a number of cognitive tests were related to the olfactory scores
	Bsteh et al[760]	2020	3	Cross-sectional	260 MS	SS-TDI Cognitive measures OCT measures	Olfactory threshold correlated with number of relapses per year before assessment and shorter disease duration Odor discrimination and ID, and their sum, correlated with longer disease duration, higher EDSS, and reduced cognitive function

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
							Peripapillary retinal nerve fiber layer thickness correlated with ID and discrimination but not threshold
	Bsteh et al[761]	2020	4	Case-control	37 MS 18 HCs	SS-TDI MRI measures	Statistical parameter matching found decreased gray matter in the anterior cingulum as well as temporal and frontal brain regions of MS relative to controls Relationship noted between SS-D+SS-I odor scores and gray matter decreases in the olfactory gyrus, anterior cingulate, and temporal regions
	Da Silva et al[762]	2020	3	Cohort	149	B-SIT MS severity scales	After a median follow-up of 121 months, those with impaired B-SIT at baseline had greater change per month during follow-up on severity scales and higher hazard of death The authors suggest that a brief odor ID test can be a marker of degeneration in MS
	Goverover et al[763]	2020	4	Case-control	23 MS 15 HCs	UPSIT® Cognitive measures	MS scored lower than HCs on UPSIT® Those with higher scores reported better mental and physical QOL and performed better on the BICAMS and Actual Reality tasks The authors suggest that olfaction may be a clinical marker for MS disability
	Okada et al[764]	2020	4	Case-control	40 relapsing-remitting MS 40 HCs	OSIT-J Cognitive measures	Lower olfactory scores in patients with relapsing-remitting MS than HCs and correlated with 3rd ventricle width The authors suggest that OI impairment is related to cognitive dysfunction and central brain atrophy

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	OuYang et al[765]	2020	4	Case-control	18 MS 20 matched HCs	fMRI to lavender and rose odorants	MS had reductions in activation in right insula, amygdala, inferior frontal gyrus, and frontomarginal gyrus, and left supramarginal gyrus
	Almasi et al[766]	2021	3	Cohort	48 MS	Sniff Magnitude Test	14.6% of the study group had OD (8.3% hyposmia and 6.3% anosma) Such dysfunction was related to longer disease duration, higher hospital administration rate, lower MMSE, and disease progression
Parkinson disease	Ansari and Johnson[767]	1975	4	Case-control	22 PD 37 sex- and age-matched HCs	Amyl acetate thresholds	Higher thresholds in PD 10 showed a significant decrease; 9 of these had moderately or rapidly progressive disease Significant negative correlation between rate of disease progression and olfactory test scores
	Ward, Hess and Calne[768]	1983	4	Case-control	72 PD 53 HCs	Phenylethylmethy carbinol and amyl acetate detection thresholds Discrimination test	PD were impaired on all olfactory tests 39% scored 2 standard deviations below the mean of the HCs 17% and none of the HCs were totally anosmic Repeated amyl acetate trials showed larger decline in PD than in HCs
	Serby et al[769]	1985	4	Case-control	5 PD 11 AD 12 alcoholics with dementia 10 alcoholics without dementia 19 young HCs 16 middle-aged HCs 20 older HCs	10-odor 2-alternative forced-choice ID test presented twice Analogous tactile test	PD and AD test scores similarly compromised relative to the other groups Only those who performed well on tactile test included to rule out dementia-related test-taking difficulties
	Quinn et al[770]	1987	4	Case-control	78 PD 40 HCs	Amyl acetate detection threshold	PD exhibited impaired threshold compared with HCs No significant correlation between threshold values and age, sex, disease duration, or drug therapy No effect of on/off dopamine therapy

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Doty et al[771]	1988	3	Case-control and cohort	81 PD 81 matched HCs	UPSIT® PEA threshold	Both UPSIT® (n = 81) and threshold values (n = 38) compromised in PD No evidence of longitudinal changes in test scores over 5- to 39-month intervals Olfactory test scores independent of a range of demographic, cognitive, and motor variables 72% of PD unaware of their deficit until being tested Comparison of PD scores to those of matched AD found no differences
	Kesslak et al[604]	1988	4	Case-control	18 AD 14 PD 14 MS 18 HCs	UPSIT® Match-to-sample task using uncommon odors	Significant loss on both tests in AD and PD but not in MS Severe impairment on match-to-sample test PD test scores lower than all other groups
	Doty et al[772]	1989	3	Cross-sectional	58 PD	UPSIT®	Performed principal component analysis on cognitive, motor, and olfactory test scores of PD revealed 6 components: cognitive/memory, gross motor, oral motor, fine motor, olfactory, and tremor These findings and those from multiple regression and canonical correlations suggest the OD of PD is independent of cognitive, perceptual-motor, and memory manifestations of the disease
	Bostantjopoul et al[773]	1991	4	Case-control	44 PD 30 HCs	Amyl acetate threshold Odor naming test	PD exhibited OD on both types of tests relative to HCs
	Murofushi et al[774]	1991	4	Case-control	18 PD 10 HCs	T&T olfactometer	Both detection and recognition thresholds elevated in PD Auditory acuity normal

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Zucco et al[775]	1991	4	Case-control	8 PD 16 elderly HCs	Short-term OM and ID test	PD were found more efficient in naming than in matching odors, whereas the opposite occurred in the elderly HCs
	Doty et al[776]	1992	4	Case-control	20 unmediated PD 20 medicated PD 20 HCs	UPSIT®	Unilateral testing found all PD to have bilateral dysfunction; asymmetries were not lateralized and unrelated to side of major motor dysfunction, and did not differ from those of HCs No influence of PD-related drugs on olfactory test scores No associations between test scores and degree of rigidity, bradykinesia, or gait disturbances
	Doty et al[777]	1992	4	Case-control	6 MPTP parkinsonism 12 matched PD 10 matched HCs	UPSIT® PEA threshold	PD, but not MPTP PD, scores lower than HCs on both tests Finding suggests that MPTP-induced parkinsonism, unlike idiopathic PD, is not accompanied by major changes in smell function
	Doty et al[778]	1993	4	Case-control	21 PD 21 PSP 21 matched HCs	UPSIT® PEA threshold	PSP is commonly misdiagnosed as PD PD, but not PSP, had major smell loss relative to HCs In both types of patients, no relationship between olfactory test scores and measures of motor symptom severity, disease stage, and medication use
	Hawkes and Shephard[779]	1993	4	Case-control	96 PD 96 HCs	UPSIT®	Confirmed significant decline in odor ID ability in PD UPSIT® item analyses suggested that 2 odorants, pizza and wintergreen, distinguished between with PD and HCs, with 66% and 47% differences from controls, respectively

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Stern et al[780]	1994	4	Case-control	9 young-onset PD 109 older-onset PD 80 benign PD 29 malignant PD 40 tremor-predominant PD 20 postual instability gait disorder PD	UPSIT®	Smell ability was compared among subtypes of PD Subtle differences occurred between benign and malignant, as well as tremor-predominant vs postural instability-gait disorder–predominant subtypes
	Doty et al[781]	1995	4	Case-control	180 PD 612 HCs	UPSIT®	Established optimal UPSIT® discrimination criteria for differentiating PD from HCs Sex and age influenced test scores
	Lehrner et al[782]	1995	4	Case-control	13 PD 13 age-matched HCs	B-threshold Odor ID, Memory SPECT imaging of DAT ligand (1231)β-CIT	PD scored below HCs on all measures SPECT imaging found no associations with olfactory measures and dopaminergic degeneration as measured by (1231)β-CIT SPECT Indicated data support previous evidence that impaired olfaction in PD is independent of motor signs and disease severity
	Wenning et al[783]	1995	4	Case-control	118 PD 29 MSA 15 PSP 7 CBD 123 HCs	UPSIT®	Differing degrees of smell loss found among a range of parkinsonian syndromes, with PD exhibiting the largest deficit Mild impairment in MSA and normal function in PSP and CBD relative to controls UPSIT® score of 25 resulted in sensitivity of 77% and specific of 85% in differentiating PD from atypical parkinsonism
	Barz et al[784]	1997	4	Case-control	13 medicated PD 18 nonmedicated PD 38 matched HCs	Odor ID, discrimination, OERP	Odor perception was compromised in PD and not influenced by medication OERP odor latencies prolonged in both PD groups Trigeminal latencies not impacted by PD or drugs

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Hawkes et al[785]	1997	4	Case-control	57 PD 47 HCs	UPSIT® OERP Postmortem pathology of 8 brains	Only 26% of the UPSIT® scores of PD fell within the level expected for 95% of the controls Pizza and wintergreen were the best discriminators, with a sensitivity of 90% and a specificity of 86% OERPs not detectable or latencies delayed in PD No correlation between test scores and disease duration LB found in every OB of autopsied cases
	Lehrner et al[617]	1997	4	Case-control	22 AD 21 PD 19 HCs	B-threshold 20-odor ID test Odor recognition test (15-minute interval)	Both AD and PD exhibited deficits on ID and threshold tests Only AD exhibited poorer OM
	Ahlskog et al[620]	1998	4	Case-control	11 pure dementia 31 parkinsonism-dementia complex 9 ALS 9 pure parkinsonism 53 Chamorro HCs 25 North American HCs	UPSIT®	Lower UPSIT® scores in dementia and the other 3 syndromes of Guamanian neurodegenerative disease The decrement in Guamanian ALS contrasts with idiopathic ALS for which smell loss reported to be minimal
	Hawkes and Shephard[622]	1998	4	Case-control	155 PD 72 MS 58 ALS 8 AD 154 HC	UPSIT® OERP	81% of PD had abnormal UPSIT® scores; 32% had prolonged OERP latencies with normal amplitudes More dysfunction was observed in PD than in the other groups
	Daum et al[786]	2000	4	Case-control	40 PD 40 HC	SS-TDI	HCs outperformed PD on all 3 components of the SS-TDI
	Montgomery et al[787]	2000a	3	Cohort	18 PD 19 HC Validation: 103 PD 122 HCs	UPSIT®	Olfaction was a component of a diagnostic test battery for PD and accounted for more variance than any other measure (48%)
	Sobel et al[788]	2001	4	Case-control	20 PD 20 HCs	UPSIT® Vanillin Threshold Propionic acid threshold	PD exhibited lower scores than HCs on all measures Additionally, increasing sniff vigor improved performance in a subset of patients who had performed most poorly

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Tissingh et al[789]	2001	4	Case-control	41 PD 18 HCs	B-SIT Discrimination Threshold	PD scored lower on all olfactory tests Negative correlation between the scores on the lengthy odor discrimination test and disease severity
	Zucco[790]	2001	4	Case-control	6 early-stage PD 12 HCs	Odor naming and matching	PD were less efficient with left nostril in matching task in those with predominant right-sided motor dysfunction
	Muller et al[791]	2002	4	Case-control	37 PD Normative controls	SS-TDI Subjective	9 of 37 PD self-reported decreased OF before diagnosis, 14 at the time or soon after diagnosis, and 14 being unaware of any smell dysfunction Testing found 19 patients with anosmia, 13 with severe hyposmia, and 5 with moderate hyposmia No correlations between test scores and disease severity or duration
	Double et al[792]	2003	4	Case-control	49 PD 52 HCs	B-SIT	Abnormal function in 82% of patients compared with 23% of HCs Only 5 of the 12 test odors needed to meaningfully discriminate PD from controls
	Hudry et al[793]	2003	4	Case-control	24 PD 24 HCs	ID intensity, hedonics familiarity, edibility ratings to 12 odors	All measures deficient in PD
	Katzenschlager et al[794]	2004	4	Case-control	18 PD 14 VP 27 HCs	UPSIT®	VP UPSIT® scores better than PD scores and did not differ from HCs, suggesting smell testing can differentiate between PD and VP
	Khan et al[795]	2004	4	Case-control	18 PD 17 early-onset PD with PARK2 mutations 11 early-onset PD without PARK2 mutations 28 HCs	UPSIT®	Mean UPSIT® score of those with PARK2 mutations (Parkin disease) did not differ from the HCs Both PD and those without PARK2 mutations had worse OF The authors suggest the possibility that Parkin disease is a distinct separate entity from PD

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Hummel et al[796]	2005	4	Case-control	11 PD (ON/OFF, deep brain stimulation)	SS-T and SS-D	No effect of deep brain stimulation on odor threshold to butanol Discrimination performance better during "on" period
	Ondo and Lai[797]	2005	4	Case-control	20 tremor-dominant PD with family history of tremor 15 tremor-dominant PD with no family history of tremor 25 nontremor PD	UPSIT®	Tremor-dominant PD without family history of tremor had same smell function as nontremor PD; however, tremor-dominant PD with a family history of tremor exhibited better function than the other groups This suggests that the latter may be more akin to patients with essential tremor for whom no smell loss is present
	Marras et al[798]	2005	3	Cohort	26 twin pairs discordant for PD 26 HCs	UPSIT® at baseline B-SIT at follow-up	At baseline, the twins with PD scored below the twins without PD The latter scored the same as HCs Follow-up on average, 7.3 years Two of 19 available previously unaffected patients converted to PD The change in test scores was greater for these 2 twins than for the 16 twins who did not develop PD Age affected smell test scores of all patients over the test-retest period
	Siderowf et al[799]	2005	3	Cross-sectional	25 early PD	UPSIT® TRODAT SPECT imaging of DAT Symptom ratings	UPSIT® scores correlated with TRODAT uptake in the striatum (r = 0.66) as well as the putamen (r = 0.74) Smell test correlations stronger than UPDRS ratings
	Lee et al[800]	2006	4	Case-control	26 PD 20 MSA 15 HCs	B-SIT	PD < MSA and HCs Significant correlation in PD between B-SIT scores and cardiac 123I-MIBG uptake Implies that functional losses of the olfactory and cardiac sympathetic systems are closely coupled in PD

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Ross et al[801]	2006	4	Case-control	17 brains with LB 147 brains without LB	B-SIT Cognitive Abilities Screening Instrument and demographics	Premortem B-SIT scores lower in cases with LB Smell is only significant measure that differs between brain types
	Bohnen et al[802]	2007	4	Case-control	27 PD 27 HCs	UPSIT® Dopamine transporter PET	UPSIT® scores lower in PD 3 odors identified with an accuracy of >0.75 for diagnosing PD Significant correlations were present between the test scores and striatal DAT activity on PET imaging
	Ferreira et al[803]	2007	3	Cross-sectional	11 LRRK2 mutation carrying PD identified from 144 unrelated PD probands	UPSIT®	9 of 11 (82%) mutation carriers exhibited impaired smell function The 2 who scored normal were from the same family Sensory complaints and daytime somnolence were present in 8 and 7 of these G2019S-positive patients, respectively
	Kim et al[804]	2007	4	Case-control	59 PD 25 HCs	B-SIT	B-SIT scores lower in PD Scores did not correlate with disease duration, stage, UPDRS scores, or olfactory sulcus depths, likely reflecting loss that precedes motor system and olfactory sulcus damage
	Lee et al[805]	2007b	4	Case-control	24 PD 15 DIP 15 HCs	B-SIT	PD < DIP; DIP = HCs B-SIT scores higher in DIP than in PD and 14 of 15 were within normal range The one outlier exhibited marked decreased cardiac MIBG uptake similar to that of PD The parkinsonism in this case was more persistent on withdrawal of the offending drug
	Quagliato et al[806]	2007	4	Case-control	50 PD 76 HCs	B-SIT	80% of PD cases had a smell deficit Lower scores noted in those initially presenting with resting tremor, rigidity, and bradykinesia

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Boesveldt et al[807]	2008	4	Case-control	404 PD 150 HCs	SS-ID SS-D	65% of PD had impaired ID and 42.1% discrimination relative to HCS Discrimination, but not ID, was correlated with disease duration ID + discrimination did not improve discrimination over ID alone
	Goldstein et al[808]	2008	4	Case-control	77 PD 57 MSA 87 HCs	UPSIT®	PD had lower mean UPSIT® scores than MSA Normal function absent in all PD and in half of MSA In PD, UPSIT® scores correlated positively with 6-[18F]fluorodopamine-derived radioactivity They propose that to clinically differentiate between PD and MSA, olfactory testing should first be performed
	Guo et al[809]	2008	3	Case-control and cohort	15 PD 15 HCs	Discrimination and ID thresholds	PD tested 6 and 12 months for smell function after implantation of bilateral electrodes in the substantia nigra Scores were compared preoperatively and postoperatively, as well as with controls and between the medication-off/stimulator-on or -off conditions Deep brain stimulation improved recognition thresholds in PD
	Hertig et al[810]	2008	3	Cohort	27 PD	SS-TDI	Patients retested over an average period of 4.4 years 4 improved significantly, 4 decreased significantly, and most remained the same
	Iijima et al[811]	2008	4	Case-control	54 PD 50 HCs	OSIT-J	Poorer performance in PD No correlations of scores with motor function, disease duration, or medication

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Lötsch[812]	2008	4	Case-control	102 PD 2076 HCs	SS-TDI	Found olfactory loss occurs in 99% of PD Principle component analysis found 1 component with high loadings from ID, threshold, and discrimination tests, and another component loading mainly with threshold
	Louis et al[813]	2008	3	Cohort	1078 community-living persons without PD or dementia	UPSIT®	Healthy persons with some smell loss were 1.55 times more likely than those without smell loss to exhibit mild parkinsonian signs—signs believed to be precursors to PD or AD 16% had mild parkinsonian signs
	Ross et al[814]	2008	3	Cohort	2267 men aged 71 to 95 years initially without clinical PD or dementia	B-SIT	Olfaction and neurological state followed for up to 8 years The odds ratio for development of PD in lowest B-SIT quartile was 5.2 compared with the top 2 quartiles This association did not continue beyond 4 years of follow-up Concluded impaired olfaction can predate the diagnosis of clinical PD by at least 4 years and may be useful in detecting persons at high risk for PD
	Shah et al[815]	2008	4	Case-control	64 tremor-dominant PD 59 ET 245 HCs	UPSIT® OERP	After controlling for confounders, only PD exhibited smell dysfunction, with ET scores being equivalent to HC scores ET with a family history of tremor scored significantly better than HCs and had a slower age-related decline, an effect not seen on OERP

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Silveira-Moriyama et al[816]	2008	4	Case-control	19 parkinsonian and 2 asymptomatic carriers of the G2019S mutation 143 sporadic PD 135 HCs	UPSIT®	Mean UPSIT® score of G2019S parkinsonian carriers < HCs and similar to that of sporadic PD 2 asymptomatic mutation carriers had normal UPSIT® scores Postmortem studies of 4 cases found α-synuclein deposition in the olfactory pathways
	Verbaan et al[817]	2008	4	Case-control	295 PD 150 HCs	SS-ID SS-D	61% of PD had impaired ID and 43% impaired discrimination No meaningful correlations with demographic or clinical variables Parkin and DJ-1 mutation carriers had normal scores ApoE genotype not related to olfactory scores
	Wilson et al[818]	2008	3	Cohort	742 community-living older adults	B-SIT	Olfactory ID score related to higher level of global parkinsonism at baseline and more rapid progression of global parkinsonism on follow-up at 5 years, particularly on gait disturbance
	Boesveldt et al[819]	2009	4	Case-control	55 PD 50 HCs	SS-T Odor recognition memory test	PD performed slightly but significantly worse than HCs on an odor recognition memory task Not present after correction for T scores, suggesting that odor recognition memory is not independently impaired in PD
	Boesveldtl et al[820]	2009	4	Case-control	52 PD 50 HCs	SS-ID (16 odor) SS-ID (32 odor) SS-D (16 odor) SS-D (32 odor) SS-T	PD scored below HCs on all tests Neither the 32-odor ID nor the 32-odor discrimination test was better at discriminating between PD and HCs than their 16-item counterparts

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
							Combining 16-odor ID test with 16-item discrimination test did not improve discrimination, but combining the 16-odor ID test with the threshold test did No other additions aided in this discrimination
	Chou et al[821]	2009	4	Case-control	44 PD 44 HCs	UPSIT®	AD-specific subset of UPSIT® items differentiated PD from HCs, but did not correlate with DAT activity
	Ferraris et al[822]	2009	4	Case-control	19 patients with sporadic PD 7 PD PINK1 homozygous 6 PD PINK1 heterozygous 12 asymptomatic PINK1 heterozygous 67 HCs	SS-TDI	ID impaired in nearly all patients (including PD and PINK1 cases) and preserved in healthy heterozygotes Threshold more preserved and discrimination more impaired in PD with PINK1 mutations than in patients with sporadic PD Alterations of detection and discrimination also observed in PINK1 asymptomatic heterozygotes
	Haehner et al[823]	2009	4	Case-control	400 PD Normative controls	SS-TDI	Overall, 97% of PD present with some degree of OD, a value that decreases to 74% when adjusted for age Odor ID was most sensitive to the PD deficit
	Landis et al[824]	2009	4	Case-control	45 PD Norms	SS-TDI 10-odor oral powders	All patients exhibited some degree of measurable orthonasal and retronasal smell dysfunction
	Miyamoto et al[825]	2009	4	Case-control	21 PD 48 RBD 34 sleep apnea 33 controls	OSIT-J	Olfactory test scores were low and equivalent in PD and RBD but were higher in the sleep apnea group
	Postuma et al[826]	2009	4	Case-control	21 PD without idiopathic RBD 34 PD with idiopathic RBD 68 iiRBD 36 HCs	B-SIT and UPSIT®	Relative to controls, patients with idiopathic RBD demonstrated substantial olfactory loss Olfaction more impaired in PD than in idiopathic RBD and did not differ between PD with, or without, idiopathic RBD

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Shah et al[827]	2009	4	Case-control	75 PD 74 HCs	UPSIT®	UPSIT® scores lower in PD than in HCs Such scores were not correlated with electrogustometric taste thresholds
	Silveira-Moriyama[828]	2009	4	Case-control	191 PD 17 PAF 14 MSA 145 HCs	UPSIT®	Mean UPSIT® score higher in HCs that in PAF or MSA; it was lower in PD than in PAF or MSA; no difference between MSA and PAF when adjusted for age, sex, and smoking Hyposmia may be a feature of PAF but to a lesser degree than that found in PD
	Wattendorf et al[829]	2009	4	Case-control	15 early PD 12 moderate PD 17 HCs	SS-ID (12 odors) MRI volume measures	Lower scores in both PD groups than in HCs, with no difference between PD groups Cortical atrophy in olfactory-related brain regions correlated specifically with OD in PD Positive correlations between olfactory performance and gray matter volume were observed in the right piriform cortex in early PD and in the right amygdala in moderately advanced patients
	Bohnen 2010[830]	2010	4	Case-control	58 PD 26 HCs	UPSIT® Acetyl-cholinesterase and monoamine brain PET	UPSIT® scores positively correlated with acetylcholinesterase activity in the hippocampus, amygdala, and neocortex and striatal monoaminergic activity Olfactory test scores correlated positively with scores on cognitive measures of episodic verbal learning
	Bovi et al[831]	2010	4	Case-control	11 PD 16 DIP 19 HCs	SS-TDI SPECT imaging of DAT	Patients with DIP and poor putamen uptake had abnormal OF, unlike DIP with normal putamen uptake

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
							Results suggest the smell deficits in DIP may be more related to dopaminergic loss than to a drug-mediated dopamine receptor blockade
	Cramer et al[832]	2010	4	Case-control	70 PD	B-SIT Apathy Evaluation Scale MMSE	Apathetic PD performed poorly on the B-SIT compared with nonapathetic PD, and test scores correlated with apathy test scores The simultaneous disruption of olfaction and emotion in PD reflect pathology in brain regions involved in both olfactory and emotional processing
	Deeb et al[833]	2010	3	Cohort	73 early PD	UPSIT® OERP DAT SPECT	The sensitivity of UPSIT® was essentially equivalent to that of DAT SPECT in identifying developing PD UPSIT® correlated moderately with DAT uptake ($r = 0.44$; $P < 0.005$) and UPDRS score ($r = 0.43$; $P < 0.05$) and weakly with symptom duration ($r = 0.25$; $P < 0.05$) OERP showed increased latency but no change in amplitude and no correlation with DAT
	Hummel et al[834]	2010	4	Case-control	8 PD 13 HCs	SS-TDI fMRI	PD had lower SS-TDI scores than controls Stimuli rated weaker and more pleasant by PD than controls during fMRI scans Both PEA and H2S stimuli were associated with lower activation in the amygdala-hippocampus complex in patients, increased PEA-related activity occurred in the striatum and the left inferior frontal gyrus In contrast, H2S led to hypoactivation of the ventral striatum in PD but not HCs and did not enhance left inferior frontal activity

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Kertelge et al[835]	2010	4	Case-control	100 PD 27 manifesting mutation carriers (15 Parkin, 17 PINK1, 8 LRRK2, 3 SNCA, 4 ATP13A2) 20 nonmanifesting mutation carriers 110 HCs	UPSIT®	Olfaction was most impaired in PD than in all other groups Within mutation carriers, carriers of 2 mutations in Parkin and PINK1 showed better UPSIT® performance than LRRK2 and SNCA carriers
	McKinnon et al[836]	2010	4	Case-control	23 suspected PD 15 possible PD 19 probable PD 37 ET 25 patients with restless legs syndrome 33 MCI 207 HCs	UPSIT®	Only probable PD differed significantly from the HCs after controlling for confounds such as age No other groups differed significantly from one another in terms of UPSIT® scores
	Meusel et al[837]	2010	3	Cohort	19 PD tested twice separated by a 5-year interval	SS-TDI OERP	Mean SS-TDI score decreased across a 5-year period, although age was not controlled and a few patients improved On the first test, 3 patients had measurable OERPs; at follow-up, none had OERPs even though most patients were not anosmic
	Oka et al[838]	2010	4	Case-control	66 PD 26 olfactory HCs 21 cardiac HCs	OSIT-J 123I-MIBG cardiac scintigraphy	PD had lower olfactory test scores than controls The OSIT-J score was related to both cardiac sympathetic and parasympathetic dysfunction, as well as vascular sympathetic dysfunction as indexed by the heart/mediastinum ratio of cardiac MIBG uptake, the fall in orthostatic blood pressure, and heart rate variability
	Ramjit et al[839]	2010	4	Case-control	58 PD 51 matched HCs	UPSIT®	Anosmia reported to be present in 96.4% of PD and 49% of HCs PD had larger decrease in systolic blood pressure from a seated to standing position than HCs

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
							Heart rate did not differ significantly Reflexive tachycardia was inversely proportional to levodopa equivalent daily dose score (p = .002) Both anosmia and constipation were correlated with disease duration
	Santin [840]	2010	4	Case-control	19 early-onset PD 51 late-onset PD 70 matched HCs	SS-ID (12 odors)	Both PD groups exhibited olfactory deficits, but those with symptoms starting before 45 years of age (early-onset PD) had better sense of smell than late-onset PD
	Sedig et al[841]	2010	4	Case-control	61 PD 51 HCs	B-SIT	Rhinorrhea is more prevalent in PD (24%, with 15% severe) than in HCs (6%, with 2% severe) B-SIT scores slightly lower in PD than in HCs (5 vs 6; 20%) The authors conclude that rhinorrhea does not impact B-SIT performance
	Silveira-Moriyama et al[842]	2010	4	Case-control	140 PD 36 progressive supranuclear palsy 126 HCs	UPSIT®	Mean UPSIT® PSP scores < HCs but > PD In PSP, UPSIT® scores correlated with MMSE but not disease duration, motor subscale of the UPDRS, or the Fullerton Advanced Balance Scale Six progressive supranuclear palsy brains were examined postmortem and all revealed neurofibrillary tangles and tau accumulation in the rhinencephalon, although only 3 had hyposmia
	Silveira-Moriyama et al[843]	2010	4	Case-control	14 PD carriers of the heterozygous G2019S LRRK2 mutation. 106 PD nonmutation carriers 118 HCs	SS-ID (16 odors)	The mean SS-ID score in LRRK2 was higher than in noncarrying PD and lower than in controls Patients with low scores tended to be younger and to have more dyskinesia, a longer disease course, and a less frequent family history of PD

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Aden et al[844]	2011	4	Case-control	87 PD 28 matched HCs	B-SIT	PD had significantly lower B-SIT scores than controls and had lower intake of polyunsaturated fatty acids and higher intake of carbohydrates In both PD and HCs, lower B-SIT scores were associated with less intake of protein and a low nutrient density of folate, magnesium, and phosphorus
	Alcalay et al[845]	2011	4	Case-control	PD group: 10 Parkin mutation heterozygotes, 9 compound heterozygotes, 25 noncarriers Unaffected family members: 18 heterozygotes, 2 compound heterozygotes, 60 noncarriers	UPSIT®	Among PD probands, compound heterozygotes had UPSIT® scores within the normal range and, thus, performed better than heterozygotes and noncarrier PD who had abnormal smell function Among family members without PD, UPSIT® performance was similar in heterozygotes and noncarriers, and better than heterozygotes with PD
	Berendse et al[846]	2011	4	Case-control	96 PD Controls: norm data	UPSIT® Multiple cognitive and motor measures	96% of PD exhibited some degree of smell loss (40% anosmic, 54% hyposmic) Weak correlations found between UPSIT® score and disease duration, disease severity, and several other measures including BDI, BAI, and daytime sleepiness score of the Scales for Outcomes in Parkinson's Disease – Sleep questionnaire
	Damholdt et al[847]	2011	4	Case-control	24 PD without dementia with B-SIT scores <5 39 PD with B-SIT scores ≥5 without dementia 29 HCs	B-SIT Cognitive tests	Those with B-SIT scores <5 had lower composite memory scores than the other 2 groups The 2 PD groups were indistinguishable on executive function but scored lower than the control group

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Iijima et al[848]	2011	4	Case-control	55 akinetic-rigid type PD 21 mixed-type PD 14 TDT PD	OSIT-J	Higher frequency of subjective symptoms of impaired smell in the akinetic-rigid type than in the tremor-dominant type group Test scores were significantly lower in the akinetic-rigid type than in the tremor-dominant type PD group
	Kim et al[849]	2011	4	Case-control	31 PD 25 HCs	B-SIT MMSE	B-SIT scores significantly lower in PD MMSE lower in PD than HCs
	Moessnang et al[850]	2011	4	Case-control	16 PD 16 HCs	SS-TDI fMRI	All elements and the composite SS-TDI scores were lower in PD than in HCs Interestingly, profound hyperactivation in the piriform and orbitofrontal cortices was observed in PD compared with a standard activation protocol of HCs
	Rodriguez-Violante[851]	2011	4	Case-control	70 PD 70 HCs	B-SIT	B-SIT differentiated PD and controls with 71.4% sensitivity and 85.7% specificity when patients were divided into 2 age groups
	Rolheiser et al[852]	2011	4	Case-control	14 PD 14 HCs	UPSIT® DTI MRI	Significant dysfunction observed in PD on UPSIT® DTI revealed significant group differences in both the substantia nigra and anterior olfactory region, with fractional anisotropy of the olfactory region clearly distinguishing PD from HCs
	Ruiz-Martinez et al[853]	2011	4	Case-control	44 LRRK2 PD 146 PD (no LRRK2)	B-SIT 123I-MIBG cardiac scintigraphy	75% (110 of 146) noncarriers exhibited hyposmia; 36% (16 of 44) carriers exhibited hyposmia The early and delayed MIBG uptake in LRRK2 carriers was superior to that of the noncarriers

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Saunders-Pullman et al[854]	2011	4	Case-control	31 LRRK2 PD 30 PD with no LRRK2 28 LRRK2 non-manifesting family members 46 HCs	UPSIT® LRRK2 genotyping	Olfaction is impaired in LRRK2 G2019S mutation–related PD, although less overall than PD with no LRRK2 mutation; however, a subset of LRRK2 mutation–carrying family members exhibit some smell dysfunction, suggesting smell loss may be a marker for PD development in this group
	Suzuki et al[855]	2011	4	Case-control	98 PD 15 MSA 7 PSP 29 HCs	OSIT-J	The mean OSIT-J score for PD was significantly lower than those for MSA, PSP, and HCs The authors suggest that the OSIT-J test may be useful clinically for both detecting OD in PD and for differential diagnosis
	Valldeoriola et al[856]	2011	4	Case-control	14 idiopathic PD 14 LRRK2 PD 13 HCs	UPSIT®	UPSIT® score was lower in both LRRK2 and PD than in HCs In LRRK2, a positive correlation was found between myocardial MIBG uptake and UPSIT® scores ($r = 0.801$, $P = 0.001$) Since MIBG cardiac reduced uptake and impaired olfaction are markers of LB pathology, these findings may reflect neuropathological heterogeneity among LRRK2
	Wang et al[857]	2011	4	Case-control	29 PD 29 HCs	T&T olfactometer MRI brain volume measures	Odor recognition thresholds elevated in PD relative to HCs PD associated with reductions in OBVs and olfactory sulcus depths Positive correlations noted between olfactory performance and OBVs in both PD and HCs

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Wu et al[858]	2011	4	Case-control	26 PD 26 HCs	Discrimination and ID thresholds MRI volume measures	12 of 26 PD (46%) had OD Function normal in HCs No meaningful correlations of smell tests with disease duration, UPDRS score part III, and disease stage Atrophy present in piriform and orbitofrontal cortices in PD
	Yoritaka et al[859]	2011	4	Case-control	6 PD with PARK2 mutations 10 HCs	SS-TDI	PD with PARK2 mutations had higher average odor thresholds than the 10 controls. No differences in ID or D.
	Zhang et al[860]	2011	4	Case-control	25 PD 25 HCs	Discrimination and ID thresholds based on average among 5 different stimuli	Fractional anisotropy values in the white matter of the left cerebellum correlated positively with odor ID thresholds; such thresholds were negatively correlated with mean diffusivity values in the white matter of the right cerebellum
	Baba et al[861]	2012	3	Cohort	44 PD without dementia	OSID-J Cognitive measures PET and MRI	10 of the 44 PD developed dementia over a 3-year period; all had baseline hyposmia Those with severe hyposmia had an 18.7-fold increase in their risk of dementia for each 1-standard deviation (2.8) decrease in the OSID-J score Severe hyposmics exhibited a characteristic distribution of cerebral metabolic decline identical to that of dementia
	Busse et al[862]	2012	3	Case-control and cohort	385 PD baseline 88 PD follow-up 132 non-PD parkinsonism	SS-ID (12 odors)	Olfactory test discriminated PD from non-PD parkinsonism at a moderate level Hyposmia less apparent in tremor-dominant PD than in akinetic-rigid and mixed type PD (55% vs 76%) Hyposmia mildly progressed from baseline to 5-year follow-up Highest diagnostic accuracy when olfaction, SN echogenicity, and motor function tests combined

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Chen et al[863]	2012	3	Case-control	110 PD 110 HCs	SS-ID (16 odors)	66.6% of PD ID scores fell below the 95% confidence interval of the ID scores of the HCs Found that autonomic dysfunction correlated with smell dysfunction in PD
	Kang et al[864]	2012	3	Case-control	15 PD 18 HCs	UPSIT® Autonomic function tests Cardiac tests Cognitive tests	Smell test scores lower in PD Scores positively correlated with pupil constriction velocity, heart failure, heart rate variability, MMSE, and activities of daily living scales, and negatively correlated with Parkinson's Disease Questionnaire-39 and gastrointestinal items of the Non-motor Symptoms Scale
	Kang et al[865]	2012	3	Cohort	98 drug-naive PD	B-SIT MMSE	PD with normal smell had higher MMSE scores; those with RBD and OD had lower MMSE scores Patients with RBD and/or hyposmia typically exhibited the akinetic-rigid PD phenotype
	Maremmani et al[866]	2012	4	Case-control	133 PD 511 HCs	Italian Odor ID test	PD scores below those of HCs for all age groups In HCs, performance decreased with age for both sexes
	Parrao et al[867]	2012	4	Case-control	44 PD 17 age-matched HCs	SS-ID and SS-D Vanillin and propionic acid thresholds Cognitive tests	PD had lower ID and discrimination scores than HCs Significant correlation between olfactory deficits and executive function measures
	Rahayel et al[868]	2012	1	Systematic review and meta-analysis	39 studies on AD 42 studies on PD	Olfactory psychophysical examinations (eg, UPSIT®, SS-TDI)	Quantitative meta-analysis indicates significant OD is evident in both AD and PD, with AD showing a more significant deficit in ID and recognition while PD had those but also had significant difficulty with detection

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Siderowf et al[869]	2012	4	Case-control	4350 normals 769 microsmics	UPSIT® Survey of prodromal PD features	26% of patients with ≥4 nonmotor features were microsmic, compared with 12% of those having ≤3 such features Smell testing may be useful in assessing risk for future neurodegeneration
	Casjens et al[870]	2013	4	Case-control	148 PD 148 HCs	SS-ID (16 odor)	83.2% PD exhibited smell dysfunction compared with 31.1% of HCs Dysfunction in PD associated with rigidity dominance and disease severity
	Hakyemez et al[871]	2013	4	Case-control	28 early-stage PD 19 HCs	UPSIT® MRI OBVs	UPSIT® scores significantly lower for PD than HCs No relation of scores to disease stage, duration, or OBVs
	Sierra et al[872]	2013	4		50 idiopathic PD 50 community controls 49 AsG2019S+ 29 G2019S-associated PD 47 non-ASG2019S carrier relatives	UPSIT®	The proportion of hyposmic individuals was not statistically different in patients with PD-G2019S (50%) and idiopathic PD (82%), but hyposmia was significantly less common in both AsG2019S+ (26%) and AsG2019S– (28%)
	Antsov et al[873]	2014	4	Case-control	50 PD 50 HCs	SS-ID (12 odors)	Average score lower in PD than in controls Cutoff of 7 gave 76% sensitivity and 86% specificity for PD diagnosis
	Cecchini et al[874]	2014	4	Case-control	61 PD 66 HCs	SS-ID (16 odors)	Test scores significantly lower in PD than in HCs
	Driver-Dunckley et al[875]	2014	4	Case-control	10 PD 13 LBD 69 HCs	UPSIT®	Postmortem autopsy compared with prior baseline UPSIT® demonstrated that both PD and LBD had lower UPSIT® scores than HCs, with PD having the lowest scores
	Gaig et al[876]	2014	4	Case-control	33 idiopathic PD 33 HCs 33 LRRK2-G2019S PD	UPSIT®	LRRK2-G2019S-PD UPSIT® scores higher than idiopathic PD scores and hyposmia was less frequent in G2019S carriers than in IPD

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
							UPSIT® scores higher in female than male LRRK2-PD Hyposmia, depression, constipation and excessive daytime sleepiness were reported to occur before the onset of classical motor symptoms in >40% of LRRK2-PD in whom these symptoms were present at the time of examination
	Picillo et al[877]	2014	4	Case-control	61 PD 61 HCs	Modified UPSIT®	UPSIT® score differentiated PD and HCs with an 82% sensitivity and 88.2% specificity
	Johansen et al[878]	2014	4	Case-control	90 de novo sporadic PD 17 LRRK2 PD 36 healthy LRRK2 carriers 15 healthy family members without LRRK2 mutation	B-SIT	Hyposmia present at time of diagnosis in sporadic PD; absent in healthy LRRK2 carriers Less pronounced in LRRK2 PD compared with sporadic PD
	Rodriguez-Violante et al[879]	2014	4	Case-control	199 PD 199 HCs	UPSIT® B-SIT SS-ID (16 odors)	Moderate agreement between predicted group membership and actual group membership was found for all tests (UPSIT® K = 0.51, SS-16 K = 0.49, B-SIT K = 0.55) Lemon, turpentine, and rose had an ID rate <25th percentile for all 3 tests Odors with a high ID rate (>75th percentile) included banana for all 3 tests, and gasoline, onion and chocolate for the UPSIT® and B-SIT
	Navarro-Otano et al[880]	2014	4	Case-control	15 PD 15 suspected VP 9 HCs	UPSIT® Cardiac MIBG	Both PD and VP scored below HCs VP with a cardiac MIBG nonsuggestive of PD were more likely to have a higher UPSIT® score

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TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Wolz et al[881]	2014	4	Case-control	167 PD 85 ET 47 other tremor	SS-TDI	PD had lower TDI scores than ET and other tremor ET and other tremor did not differ from one another TDI and ID scores were related to the absence or presence of PD in tremor patients
	Guducu et al[882]	2015	4	Case-control	12 unmedicated PD 12 HCs	SS-TDI Chemosensory event-related potentials entropy measures	PD lower than HCs on all SS measures PEA and H2S induced entropy changed among time windows only for HCs
	Mahlknecht et al[883]	2015	3	Cohort	34 patients with RBD	SS-TDI	The SS-TDI score as well as the ID subdomain had a diagnostic accuracy of predicting conversion to LBD of 82.4% relative risk for LBD in the lowest tertile of OF was 7.3 compared with the top 2
	López Hernández et al[884]	2015	4	Case-control	30 PD 21 ET 47 HCs	SS-ID (12 odor) Transcranial ultrasound hypere-chogenicity of substantia nigra	Prevalence rates of hyposmia and substantia nigra hyperechogenicity were 70% and 83.3% in PD, 33.3% and 9.5% in ET, and 17% and 10.6% in HCs Both markers were present in 63% PD, no ET, and in 2 HCs
	Paschen et al[885]	2015	4	Case-control	52 PD 31 matched HCs	SS-TDI MRI OBV	No difference in MRI-determined volumes of OBs between PD and HCs No relationship between test scores and volumes
	Rossi et al[886]	2015	4	Case-control	30 PD without major depressive disorder 30 PD with major depressive disorder 29 major depressive disorder 30 HCs	SS-TDI	No differences in smell function between PD and major depressive disorder, suggesting depression does not contribute to smell dysfunction of PD

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Shill et al[887]	2015	4	Case-control	75 PD 579 HCs	UPSIT®	Hyposmia was present in 75% of PD and 25% of HCs 16% of PD unaware of smell loss; 47% of the HCs were also unaware
	Evans and Chai[888]	2016	3	Cohort	291 PD	SS-ID (12 odor) Depression and Constipation Questionnaire	Lower ID tests combined with reports of depression and constipation independently predicted LB PD Concluded PD cannot be reliably differentiated clinically from other causes of Parkinsonism
	Fullard et al[889]	2016	3	Cohort	423 PD	UPSIT® Normative HC data Cognitive measures	90.8% exhibited some degree of dysfunction at baseline (34.8% anosmic, 28.6% severe microsmia, 27.4% mild to moderate microsmia) Those in lowest tertile had more cognitive impairment (37.4%) than those in the middle (24.4%) and highest tertiles (14.2%) Aβ1-42 was significantly lower, and tau/Aβ1-42 ratio higher in those with worse olfaction Lower UPSIT® score was associated with greater decline in MoCA score over time
	Huang [890]	2016	4	Case-control	54 PD 54 RBD 54 HCs	SS-ID (12 odors)	Olfaction more impaired in PD than in RBD and HCs RBD more impaired than HCs
	Mahlknecht et al[891]	2016	4	Case-control	646 PD 606 HCs 75 atypical PD or ET 24 RBD	SS-ID (16 odors) SS-ID (8 odors)	Odor performance lower in PD than HCs and all other cohorts
	Swallow et al[892]	2016	3	Cohort	1719 recent PD onset	UPSIT® SS-ID (16 odor)	72.2% hyposmic, 43.3% RBD, 22.1% depression, 21.5% constipation
	Barber et al[893]	2017	4	Case-control	119 PD 171 RBD 296 HCs	SS-ID (16 odor)	PD and RBD had ID impairments relative to HC. PD ID scores were slightly worse than RBD. PD and RBD equally impaired on SS-ID and cognitive tests.

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Cozac et al[894]	2017	4	Case-control	54 PD 21 HCs	SS-ID (12 odor) Cognitive measures Electroencephalography	In PD, decreases noted in SS-ID, Wisconsin Card Sorting Test, Trail Making Test time for part A, Semantic verbal fluency test, and alpha/theta ratio In PD sample, SS-ID correlated with age, disease duration, UPDRS-III, and UPDRS-III items related to gait and axial rigidity
	Iannilli et al[895]	2017	4	Case-control	17 PD 20 hyposmic non-PD 13 anosmic non-PD 21 nonanosmic	SS-TDI (for group classifications)	Electroencephalography global field power found measurable differences between PD and other study groups, indicating different pattern of CNS olfactory processing in PD
	Krismer et al[896]	2017	4	Case-control	67 PD 23 MSA 23 PSP 41 HCs	SS-TDI	PD performed significantly worse in olfactory testing than HCs and MSA or PSP No significant difference in test scores between MSA and PSP patients
	Passali et al[897]	2017	4	Case-control	78 PD Normative comparisons	SS-TDI Cognitive and motor measures	91.0% exhibited measured smell loss, compared with 55.5% of subjective assessments Subjective hyposmia, dyspepsia, constipation, and bloating differed among groups, being higher in anosmics and hyposmics than normosmics
	Terroba Chambi et al[898]	2017	3	Cohort	210 PD	SS-TDI Diagnosis prediction	At 2-year follow-up, levodopa challenge with olfactory test scores was more accurate in identifying true PD than without test scores
	Wang et al[899]	2017	4	Case-control	33 Parkin PD 49 gene-negative PD 34 HCs	SS-ID (12 odors)	33 Parkin PD performed better than panel negative patients, but still worse than HCs The differences persisted after adjusting for confounders
	Camargo et al[900]	2018	4	Case-control	42 PD 38 HCs	SS-ID (12 odors) Cognitive measures	OD prevalence in PD was 95.2%; attentional deficits correlated with olfactory loss in PD

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Dolatshahi et al[901]	2018	3	Cohort	112 PD 110 HCs	UPSIT® RBD-Screening Questionnaire scores CSF α-synuclein t-tau p-tau Aβ1-42	Baseline RBD-Screening Questionnaire scores but not MoCA, UPDRS III, or UPST scores were predictive of longitudinal increase in α-synuclein levels
	Lee et al[902]	2018	2	Cross-sectional	196 de novo PD	SS-TDI Serum uric acid levels Neurocognitive measures	Olfactory scores related to cognitive scores but not serum uric acid levels
	Li et al[903]	2018	2	Cross-sectional	159 PD	SS-ID (12 odor) Depression scales	No significant relationship was found between SS-ID test scores and either the BDI-II or GDS-30 depression measures, although color vision, as measured by the Farnsworth-Munsell 100 Hue Test, was associated with such scores
	Masala et al[904]	2018	4	Case-control	96 PD 51 HCs	SS-TDI MoCA Starkstein Apathy Scale PD Fatigue Scale UPDRS	Olfactory scores much lower in PD Both apathy and UPDRS scores correlated with degree of smell loss
	Park[905]	2018	4	Case-control	37 cognitively normal PD 29 PD with MCI	SS-TDI Cognitive test battery	PD with MCI have greater OD
	Roos et al[906]	2018	4	Case-control	63 PD Normative data	SS-TDI Body mass index	68% evidenced hyposmia Correlation of 0.26 found between olfactory test scores and body mass index
	Cecchini et al[907]	2019	4	Case-control	50 PD 50 HCs	SS-TDI Cognitive test battery	Poor olfaction in PD associated with age, cognition, apathy and visio-spatial dysfunction
	Leonhardt et al[908]	2019	4	Case-control	124 PD without dementia 154 elderly HCs	SS-ID (16 odors)	79% of PD had impairment vs 7.1% HCs 52% of PD and 6% of HCs overrated their smell ability
	Lin et al[909]	2019	4	Case-control	24 PD with hyposmia 19 PD without hyposmia	SS-ID (16 odors) OERP MoCA	No OERP differences between PD with and without hyposmia; N1 latency and P1 amplitude related to executive functions in hyposmic group

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
	Melis et al[910]	2019	4	Case-control	131 PD 118 HCs	SS-ID (16 odors)	PD scored below HCs OBPIIa gene polymorphism related to olfactory deficits in female PD Those with 2 sensitive alleles (AA) performed better than those with at least 1 insensitive allele (G)
	Pekel[911]	2019	4	Case-control	31 PD 31 HCs	SS-ID (12 odors) B-threshold	SS-ID scores lower in PD than in HCs 90% of PD and 55% of HCs were reportedly anosmic
	Pinkhardt et al[912]	2019	4	Case-control	80 PD (39 Chinese and 41 German) 170 HCs (70 Chinese and 100 German)	SS-ID (12 odors)	SS-ID scores lower in PD than in HCs Sensitivity and specificity of the German version was 75% and 98%, respectively The corresponding values for the Chinese version were 59% and 97%
	Saatci et al[913]	2019	4	Case-control	45 PD 40 HCs	SS-TDI	Reports that deep brain stimulation improves OF although controls were not matched for the same degree of OF and no PD controls provided
	Sanjari[914]	2019	4	Case-control	17 prodromal PD 18 early PD	UPSIT® Diffusion MRI connectivity measures	UPSIT® scores did not differ significantly between the 2 groups; however, based on quantitative anisotropy studies, they appear to have different white matter fiber architecture Thus, the OD in prodromal and early clinical phases of PD may involve distinct pathogenesis Increased network connectivity in prodromal and early PD could be caused by neural compensation
	Sobhani et al[915]	2019	4	Case-control	85 de novo PD 36 HCs	UPSIT® Diffusion MRI connectivity	PD scores below HC scores PD had most fibers with decreased connectivity in left inferior longitudinal fasciculus, bilateral fornix, bilateral middle cerebellar peduncle, bilateral cingulum, bilateral corticospinal tract and body, genu, and splenium of corpus callosum

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
							Such microstructural degenerative changes could underlie the clinical phenotype of prodromal PD.
	Sui et al[916]	2019	1	Systematic review and meta-analysis	3272 PD with hyposmia 5288 HCs	Psychophysical examinations (eg, UPSIT® and SS-TDI) and cognitive testing for PD diagnosis	Quantitative meta-analysis indicated a 3.84-fold increase in risk for developing PD in patients with hyposmia compared with HCs
	Wang [917]	2019	4	Case-control	56 PD with OD 44 PD without OD		PD with OD exhibited more anxiety and gastrointestinal and urinary symptoms
	Guo et al[918]	2020	4	Case-control	103 PD with OD 66 PD without OD	SS-TDI CSF α-synuclein and Aβ1-42 levels	α-Synuclein levels higher in those with OD and negatively correlated with olfactory test scores, as are Aβ1-42 levels
	He et al[919]	2020	3	Case-control and cohort	105 hyposmic PD 59 normosmic PD	SS-TDI Cognitive and other tests	2-year follow-up found hyposmic PD to have worse clinical course, with more dopamine repletion, and poorer scores on UPDRS III and MMSE
	Löhle et al[920]	2020	3	Cohort	30 untreated denovo PD	SS-TDI 18Fluorodopa PET uptake	Olfactory test scores not correlated with striatal 18Fluorodopa uptake, but with dopamine turnover presynaptic compensatory processes
	Schmidt[921]	2020	4	Case-control	64 PD 33 age-matched HCs	SS-TDI Self-assessment	SS-TDI differs significantly between groups; self-assessment had low accuracy in identifying PD
	Solla et al[922]	2020	4	Case-control	99 PD 69 HCs	SS-TDI	Males scored below females in PD Sex and apathy were predictors of SS-TDI score
	Yoo et al[923]	2020	3	Cohort	228 drug-naive PD	B-SIT Motor and cognitive tests 18F-FP-CIT PET imaging	At time of diagnosis, 59.6% had some degree of hyposmia and 21.1% were anosmic Baseline OD unrelated to motor deficits, but was related to cognitive dysfunction and prognosis

(Continues)

TABLE VII.12 (Continued)

Topic	Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
							Anosmics had higher conversion rate to dementia than either hyposmics or normosmics independent of baseline motor deficits and cognitive status
	Zhou et al[924]	2020	4	Case-control	500 PD 115 HCs	SS-TDI	ID as good as TDI in differentiating between patients with PD and HCs In PD, age and cognition together explained 7.5% of the variance of the threshold score Age, cognition, and sex explained 15.2% of the variance of the discrimination score Cognition, age, ability of daily living, and sex together explained 11.1% of the variance of the ID score

AD = patients with Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognitive; ADAS-Jcog = Alzheimer's Disease Assessment Scale – Cognitive (Japanese version); ADD = patients with Alzheimer disease dementia; ALS = patients with amyotrophic lateral sclerosis; aMCI = amnestic mild cognitive impairment; ApoE = apolipoprotein E; AROMA = Affordable, Rapid, Olfactory Measurement Array; BICAMS = The Brief International Cognitive Assessment for Multiple Sclerosis; BNT = Boston Naming Test; BOMCT = Blessed Orientation Memory Concentration Test; B-SIT = Brief Smell Identification Test; CAMCOG = Cambridge Cognitive Examination; CBD = patients with corticobasal degeneration; CD = cognitive decline; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CSF = cerebrospinal fluid; CSIT = Chinese Smell Identification Test; DAT = dopamine transporter; DIP =patients with drug induced parkinsonism; DLB = patients with dementia with Lewy bodies; DRS =Dementia Rating Scale; DTI = diffusion tensor imaging; EDSS = Expanded Disability Status Scale; ET = patients with essential tremor; fMRI = functional magnetic resonance imaging; FDG = F-Fluorodeoxyglucose; FTD = patients with frontotemporal dementia; H2S = hydrogen sulfide; HAND = HIV-associated neurocognitive disorders; HC = healthy control; HRS = Hyposmia Rating Scale; ID = identification; LB = Lewy bodies; LBD = Lewy body disease; LOE = level of evidence; LRRK2 = leucine-rich repeat kinase 2; MCI = mild cognitive impairment; MD = major depression; MIBG = metaiodobenzylguanidine; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI = magnetic resonance imaging; MS = patients with multiple sclerosis; MSA = patients with multiple system atrophy; naMCI = nonamnestic mild cognitive impairment; NPH = patients with normal pressure hydrocephalus; OB = olfactory bulb; OBV = olfactory bulb volume; OD =olfactory dysfunction; OERP = olfactory event-related potentials; OI = olfactory impairment; OM = odor memory; OPID = Odor Percept Identification; OSIT-J = Japanese Odor Stick Identification Test; PAF = patients with pure autonomic failure; PBT = _____; PD = patients with Parkinson disease; PDD = Parkinson's disease with dementia; PEA = phenylethyl alcohol; PET = positron emission tomography; PSP = patients with progressive supranuclear palsy; PST = Pocket Smell Test; RBD = patients with rapid eye movement sleep behavior disorder; SCD = patients with subjective cognitive decline; SCZ = patients with schizophrenia; SDOIT = San Diego Odor Identification Test; SMI = patients with subjective memory impairment; SOIT = Scandinavian Odor-Identification Test; SPECT = single-photon emission computerized tomography; SRT = Selective Reminding Test; SS =Sniffin' Sticks; SS-D = Sniffin' Sticks discrimination only; SS-I = Sniffin' Sticks identification only; SS-T = Sniffin' Sticks threshold only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; TDI = threshold, discrimination, identification; UPDRS = Unified Parkinson's Disease Rating Scale; UPSIT® = University of Pennsylvania Smell Identification Test; VD = patients with vascular dementia; VP = vasular parkinsonism.

processing in ADHD reveals a generally small magnitude and homogeneous pattern of deficits among 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 OF in ADHD suggests that: (1) being male, (2) having lower intellectual skills, and (3) the use of psychotropic medication were related to greater olfactory impairment.

OD is prominent in many neurodevelopmental disorders with neurotransmitter disruption.

The following statements can be made about OD: Robust, homogenous deficits in OF are common in patients with schizophrenia and these deficits do not correlate with sex, medication status, or smoking.

Aggregate grade of evidence: B (Level 1: three large quantitative meta-analytic studies that are consistent and one qualitative review).

TABLE VII.13 Section evidence summary: Related to neurotransmitter disease states

Author	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Moberg et al[952]	1999	1	Systematic review	787 patients with a *DSM* diagnosis of schizophrenia 662 HCs	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI)	Quantitative meta-analysis indicates substantial olfactory deficits, among all domains, are observed in patients with schizophrenia The influences of sex, medication status, and smoking on effect sizes were not significant among studies
Nguyen et al[953]	2010	2	Systematic review	Patients with a *DSM* diagnosis of schizophrenia HCs	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI); neuroimaging	Qualitative review indicating significant olfactory impairment in patients with schizophrenia with discussion of neuroanatomical substrates
Moberg et al[954]	2014	1	Systematic review	4491 patients with a *DSM* diagnosis of schizophrenia 875 genetic and clinical patients at-risk for schizophrenia 4408 HCs	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI)	Quantitative meta-analysis indicates robust olfactory deficits in patients with schizophrenia and at-risk youths Olfactory measures may be a useful marker of schizophrenia risk status
Tonacci et al[951]	2017	2	Systematic review	Patients with ASD HCs	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI)	Qualitative review indicating possible olfactory impairment in patients with ASD and other developmental disorders
Crow et al[955]	2020	1	Systematic review	320 patients with ASD 208 patients with OCD 320 patients ADHD 910 HCs	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI)	Quantitative meta-analysis indicates that OD is evident in individuals with ASD and OCD, with small to negligible effects in patients with ADHD

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; OCD = obsessive-compulsive disorder; HC = healthy control; LOE = level of evidence; OD = olfactory dysfunction; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

TABLE VII.14 Section evidence summary: Related to seizures or epilepsy

Author	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Kurshid et al[956]	2019	2a	Systematic review and meta-analysis	912 patients with epilepsy 794 HCs	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI)	Quantitative meta-analysis indicates significant olfactory deficits in patients with epilepsy, most prominent in TLE and mixed-frontal epilepsy
Hwang et al[957]	2020	3a	Systematic review without meta-analysis	Patients with TLE Patients with other forms of epilepsy	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI)	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[958]	2003	4	Case series	217 Chinese patients who underwent temporal lobectomy for medically intractable TLE	Resolution of olfactory symptoms Resolution of seizures Clinical characteristics of patients with olfactory aura	Resolution of olfactory auras after mesial temporal lobectomy in all patients

HC = healthy control; LOE = level of evidence; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TLE = temporal lobe epilepsy; UPSIT® = University of Pennsylvania Smell Identification Test.

OD is prevalent and may be a core deficit in patients with ASD and OCD but not those with ADHD.

Aggregate grade of evidence: C (Level 4: one moderately sized quantitative meta-analytic study and one qualitative review).

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 OF or sensitivity, and intolerance to odors, particularly during acute attacks.

Olfactory hallucinations have been recognized as a potential feature 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 and mixed-frontal epilepsy. Among patients with epilepsy, sex, age, smoking status, education, handedness, and age of illness onset were significantly correlated to olfactory performance.[947]

In a systematic review performed among patients with temporal lobe epilepsy, Hwang et al[948] found that olfactory testing could be used to differentiate temporal lobe epilepsy 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.[949] Less than 20% of patients with temporal lobe epilepsy experience olfactory hallucinations, and it is not necessarily more common than motor or sensory auras.[950] 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 OB and become activated during functional MRI (fMRI) in response to odor intensity.[951] In a study of 12 patients with temporal lobe epilepsy with olfactory auras

TABLE VII.15 Section evidence summary: Related to primary headache syndrome

	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Terrin et al[978]	2020	1b	Systematic review and meta-analysis	128 patients with MA 5 patients with MO 31 patients with ETTH 21 patients with MO and ETTH 7 patients with MA and ETTH 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[971]	2011	3b	Prospective case-control	Patients with MO Patients with MA HCs	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI)	Comparison between groups demonstrated osmophobia in 63% of MO and MA groups, with patients with MA having a worsened aversion than patients with MO to all scents 91% of migraine patients had normal smelling ability
Whiting et al[986]	2015	3b	Prospective case-control	50 patients with migraine 50 HCs	Olfactory psychophysical tests (eg, UPSIT® and SS-TDI)	Migraine patients did not have a significant difference in olfactory ability during their attacks vs in between attacks, but they were more likely to have abnormal olfactory acuity compared with controls
Aktürk et al[987]	2019	3b	Prospective case-control	Patients with MO Patients with MA HCs	OBV and OSL on MRI	Comparison between groups demonstrated significantly decreased OBVs in patients with migraine (both MA and MO) compared with HCs There was no difference seen in OSL
Stankewitz et al[964]	2011	4	Case-control	20 migraine patients Sex- and age-matched HCs	Amygdala activation on fMRI	Amygdala activation during migraine in response to olfactory stimulation
Demarquay et al[965]	2008	4	Case-control	11 migraineurs with olfactory hypersensitivity and 12 controls participated in a H(2)(15)O-PET study	Regional cerebral blood flow	Higher regional cerebral blood flow in the left piriform cortex and anterosuperior temporal gyrus in migraineurs compared with controls during both olfactory and nonolfactory conditions

ETTH = episodic tension-type headache; HC = healthy control; fMRI = functional magnetic resonance imaging; LOE = level of evidence; MA = migrainous headache with aura; MO = migrainous headache without aura; MRI = magnetic resonance imaging; OBV = olfactory bulb volume; OSL = olfactory sulcus length; PET = positron emission tomography; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

TABLE VII.16a Section evidence summary: Related to congenital causes

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Harris et al[994]	2006	2	Cross-sectional	Outpatients with OD	Subjective and objective (ODT, OIT, and SDOIT)	Patients with ICA and trauma present with the poorest OD scores
Fonteyn et al[996]	2014	3	Retrospective cohort review (patients, single-center)	Patients with nonsinonasal OD	Subjective and objective (SS-TDI)	Total anosmia rate of 93.1% in ICA
Abolmaali et al[998]	2002	4	Case-control	Patients with ICA vs controls	MRI findings	Depth of olfactory sulcus on MRI reflects presence of olfactory tract
Aiba et al[1015]	2004	4	Case series	Patients with ongenital anosmia	MRI findings	MRI can identify abnormalities in patients with ICA
Croy et al[993]	2012	4	Case-control	Patients with ICA vs controls	Subjective (QOL questionnaires)	ICA associated with increased social insecurity, depression, accidents
Cui et al[1017]	1997	4	Case-control	Patients with ICA vs controls	UPSIT®, ODT, ERP	Olfactory-evoked potentials provide a measure of OF
Dahmer-Heath et al[1012]	2020	4	Case-control	Patients with renal ciliopathies	U-Sniff and SS-ID	Underlying gene mutations (eg, TMEM67) increases risk of hyposmia
Hauser et al[1013]	2018	4	Case series	Pediatric patients with OD	Etiology, utility of imaging	MRI has higher utility than CT in evaluating ICA
Henkin et al[1019]	2016	4	Noncontrolled	Patients with ICA	Improvement in smell function on theophylline	Oral theophylline may restore OF in some forms of ICA
Karstensen et al[1000]	2018	4	Case-control	Patients with ICA vs controls	Objective (SS-TDI and MRI)	Characteristic relationship between volumetric MRI findings and OD
Kim et al[1018]	2020	4	Retrospective cohort review	Patients with hyposmia	Objective (CCCRC test and B-SIT)	0% recovery for patients with ICA
Leopold et al[1002]	1992	4	Case series	Patients with presumed ICA	Objective (olfactory ensheathing cell–conditioned medium) and biopsies	ICA associated with abnormality or absence of olfactory neuroepithelium
Peter et al[1001]	2020	4	Case-control	Patients with ICA vs controls	Objective (MRI findings)	Characteristic MRI findings with ICA
Powell et al[1014]	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[1016]	2010	4	Retrospective case series	Patients with ICA	Objective (T&T olfactometer, ERP, CT, MRI)	Total ansomia is most common in patients with ICA MRI can be helpful in diagnosis

(Continues)

TABLE VII.16a (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Schriever et al[992]	2020	4	Retrospective case series	Patients with hyposmia	Chart review of etiology	Two thirds of children with OD have ICA, but it becomes progressively less common into adulthood
Shushan et al[1020]	2015	4	Case-control	Patients with ICA vs controls	fMRI with odor stimulus	fMRI activity in patients with ICA suggests odor may be subclinically perceived

CCCRC = Connecticut Chemosensory Clinical Research Center; CT = computed tomography; ERP = event-related potential; fMRI = functional magnetic resonance imaging; ICA = isolated congenital anosmia; LOE = level of evidence; MRI = magnetic resonance imaging; OD = olfactory dysfunction; ODT = odor detection threshold; OF = olfactory function; OIT = odor identification test; QOL = quality of life; SDOIT = San Diego Odor Identification Test; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; UPSIT® = University of Pennsylvania Smell Identification Test.

(two of which exclusively had structural lesions in the amygdala on neuroimaging), all patients had resolution of olfactory symptoms after mesial temporal lobectomy.[949] The prevailing view is that these changes explain change in smell and olfactory hallucinations,[950] but another possibility is that changes in the OB play a role.[952]

Patients 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.[953,954]

Because of 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.

OD can be present in patients with epilepsy

Aggregate grade of evidence: B (Level 2: one study; Level 3: one study; Level 4: one study).

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.

Our emerging understanding of its pathophysiology suggests multiple reasons for the olfactory changes that have been described in migraine. Functional changes in the limbic system,[954] cortical spreading depression in the piriform cortex,[955,956] activation of the amygdala,[957] and the release of calcitonin gene–related peptide by olfactory stimuli[958] are among the factors that may explain this relationship. In one MRI study, patients with migraine and osmophobia had lower OBVs than controls.[959] While most patients with migraine have normal olfaction,[960,961] it may be impaired in a minority of patients, especially in deeply affected patients.[962,963]

Osmophobia is the fear, dislike, or aversion to odors. Prior literature has cited osmophobia as being present in patients with migrainous headaches with up to 95% prevalence, and yet it is not mentioned in the *International Classification of Headache Disorders* (*ICHD*).[964] Photosensitivity/photophobia and phonosensitivity/phonophobia are mentioned and noted as part of the diagnostic criteria, yet osmophobia is not, perhaps because of lower prevalence. Whether it is truly present in such a large proportion of patients with migraine is debated, but osmophobia is a common associated symptom of migraine in patients of all ages,[965,966] with a prevalence of 25% to 86% found in various clinical studies[967,968] A prospective study was performed in migrainous patients with and without aura, as well as in patients with episodic tension-type headache. A total of 67.2% of migraineurs reported osmophobia in at least a quarter of their attacks, whereas zero patients with episodic tension-type headache reported this as a symptom, suggesting that osmophobia is a highly specific symptom that can be used to differentiate migraine without aura and episodic tension-type headache.[969] This hypersensitivity to odors and even tastes may persist between attacks.[970,971] Olfactory stimuli such as smoke or perfume can precipitate migraine attacks[972] and pleasant odors such as lavender may improve it.[974,975] Osmophobia is most common in patients with migraine, but has also been reported in patients with other headache disorders such as cluster headache.[976]

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.[962] However, there are also data demonstrating that baseline olfactory acuity is more abnormal in migraine patients compared with controls,[977] as well as evidence suggesting that OBV is diminished in patients

TABLE VII.16b Section evidence summary: Related to extremely low or high BMI

	Author	Year	LOE	Study design	Study groups	Olfactory test method used	Conclusions
Related to extremely high BMI							
	Guild[1052]	1956	5	Observational, cross-sectional, case-control	Obese patients (n = 5) Controls (n = 5, all women)	Blast-injection method by Elsberg and Lewy	There was evidence that controls had greater olfactory acuity than obese patients
	Richardson et al[1068]	2004	4	Observational, cross-sectional, case-control	Patients with BMI <45 (n = 47 women/8 men) Patients with BMI >45 (n = 40 women/6 men)	B-SIT	Morbidly obese individuals were more likely than moderately obese individuals to demonstrate B-SIT scores consistent with OD
	Simchen et al[1055]	2006	4	Observational, cross-sectional, case-control	Overweight patients (n = 87) Controls (n = 226) Five age groups at intervals of 15 years, with 50 to 60 participants each, all were aged ≥20 years	ETOC	Age-dependent association between BMI and OF: odor detection and identification function were lower in overweight patients than in controls when the age was <65 years, whereas in patients ≥65 years, functions were better in overweight patients than in controls
	Trellakis et al[1053]	2010	4	Observational, cross-sectional, case-control	Obese patients (n = 12) Controls (n = 10) Overweight patients (n = 9)	SS-TDI	No significant difference in overall OF was observed in relation to BMI
	Zijlstra et al[1054]	2011	4	Observational, cross-sectional, case-control	Overweight/obese (n = 21 women/6 men) Controls (n = 21 women/6 men)	Retronasal aroma release using spiced rice	There were no significant differences in recognition of retronasal aroma release between the groups
	Skrandies et al[1040]	2015	3b	Observational, cross-sectional, case-control	Obese patients (n = 7) Overweight patients (n = 18) Controls (n = 30) Low weight patients (n = 5)	SS-TDI	Higher BMI was associated with worsened odor threshold function

(Continues)

TABLE VII.16b (Continued)

Author	Year	LOE	Study design	Study groups	Olfactory test method used	Conclusions
Stafford and Whittle[1056]	2015	4	Observational, cross-sectional, case-control	Obese patients (n = 9 women/11 men) Controls (n = 15 women/5 men)	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[1041*]	2016	3b	Observational, cross-sectional, case-control	Obese patients (n = 59) Controls (n = 36, all women)	SS-TDI	Overall OF was clearly impaired in the obese patients compared with the controls
Fernandez-Garcia[1045*]	2017	3b	Observational, cross-sectional, case-control	Morbidly obese patients (n = 46) Obese patients (n = 28) Overweight patients (n = 12) Controls (n = 77) Low weight patients (n = 17, all women)	SS-TDI	Obese patients had significantly lower overall OF compared with the control group
Uygun et al[1048]	2019	3b	Observational, cross-sectional, case-control	Obese patients (n = 52) Controls (n = 15, all women)	SS-ID + CCCRC olfactory test Butanol threshold	Obese women had lower odor identification function compared with the control group
Zhang et al[1049†]	2019	3b	Observational, cross-sectional, case-control	Obese patients (n = 15 women/20 men) Controls (n = 15 women/20 men)	OLFACT	Obese patients had lower olfactory threshold function compared with the control group
Besser et al[1046]	2020	3b	Observational, cross-sectional, case-control	Obese patients (n = 11 women/4 men) Controls (n = 47 women/27 men)	SS-TDI	Overall OF declined with rising BMI
Herz et al[1043]	2020	3b	Observational, cross-sectional, case-control	Obese patients (n = 12 women/15 men) Controls (n = 12 women/14 men)	SS-TDI	Adolescents with a higher BMI had higher ofactory threshold function compared with the control group
Poessel et al[1051]	2020	3b	Observational, cross-sectional, case-control	Obese patients (n = 14 women/14 men) Overweight patients (n = 5 women/6 men) Controls (n = 14 women/14 men)	SS-TDI	There was no statistically significant difference between weight groups with regard to measured OF

(Continues)

TABLE VII.16b (Continued)

Author	Year	LOE	Study design	Study groups	Olfactory test method used	Conclusions
Poessel et al[1044]	2020	3b	Observational, cross-sectional, case-control	Obese patients (n = 11f/13m) Overweight patients (n = 12 women/13 men) Controls (n = 14 women/12 men)	SS-T	No statistically significant difference between obese, overweight, and control patients regarding odor thresholds
Nettore et al[1050]	2020	4	Observational, cross-sectional, case-control	Obese patients (n = 92 women/48 men) Overweight patients (n = 92 women/48 men) Control patients (n = 92 women/48 men)	Flavor identification test consisting of a series of 20 aromatic extracts and one blank	BMI inversely correlated with the number of correctly identified flavors The number of correctly identified flavors was significantly higher in control patients compared with obese patients
Boesveldt et al[1058]	2011	4	Observational, cross-sectional, population-based	Population (n = 1550 women/1455 men), with a mean age of 69.3 years and mean BMI of 29.1 (range, 14.1–75.6)	SS-ID (5-item)	There was a positive correlation between correctly identified odors and BMI
Liu et al[1059]	2020	3b	Observational, longitudinal, population-based	BMI <25 kg/m^2 (n = 76) BMI 25–30 kg/m^2 (n = 970) BMI >30 kg/m^2 (n = 558) 1189 women/1110men), with a mean age of 75.6 years for all participants	B-SIT	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[1061]	2000	4	Observational, cross-sectional, case series	Obese patients (n = 15 women/15 men)	Blast-injection method by Elsberg and Lewy	Obese children had significantly lower thresholds of detection and of identifying odors compared with normative data
Richardson et al[1068]	2012	4	Intervention, cohort	Morbidly obese patients (n = 50 women/5 men) Controls (n = 32 women/8 men)	B-SIT	Larger percentage of morbidly obese patients scored within the OD range compared with the control group Gastric bypass surgery did not influence OF

(Continues)

TABLE VII.16b (Continued)

Author	Year	LOE	Study design	Study groups	Olfactory test method used	Conclusions
Enck et al[1069]	2014	3b	Intervention, cohort	Morbidly obese patients (n = 4 women/4 men) Controls (n = 22 women/22 men)	SS-TDI	Obese patients had significantly lower overall OF compared with the control group Bariatric surgery did not change odor sensitivity
Jurowich et al[1062]	2014	3b	Intervention, cohort	Morbidly obese patients (n = 29 women/13 men) Patients were divided into three groups according to the surgery that they received	SS-TDI	The morbidly obese group with the highest mean BMI had the lowest overall OF Patients who received sleeve gastrectomy surgery improved significantly postoperatively
Holinski et al[1063]	2015	3b	Intervention, cohort	Morbidly obese patients (n = 29 women/15 men) Controls (n = 15 women/8 men)	SS-TDI	Obese patients had significantly lower overall OF compared with the control group In morbidly obese patients, OF increased significantly after laparoscopic bariatric surgery
Hanci et al[1066]	2016	3b	Intervention, cohort	Obese patients (n = 32 women/22 men)	SS-TDI	Median score of obese patients was within the OD range compared with normative data OF increased signficantly after laparoscopic sleeve gastrectomy
Zerrweck et al[1064]	2017	4	Intervention, cohort	Morbidly obese patients (n = 16 women/5 men)	PST	The probability of having severe or total anosmia in obesity was extremely low OF increased signfificanlty after laparoscopic gastric bypass surgery
Campolo et al[1067]	2020	4	Observational, cross-sectional, case series	Obese patients (n = 31 women/29 men)	SS-TDI	Among middle-aged patients with stage I and II obesity, OD was highly prevalent with respect to normative age- and sex-adjusted cutoffs

(Continues)

TABLE VII.16b (Continued)

	Author	Year	LOE	Study design	Study groups	Olfactory test method used	Conclusions
	Melis et al[1065]	2021	4	Intervention, cohort	Patients undergoing bariatric surgery (n = 36 women/15 men)	SS-ID (16-item)	The OF of participants improved after bariatric surgery
	Peng et al[1039]	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[1035]	1995	4	Observational, cross-sectional, case-control	Patients with AN (n = 11) Controls (n = 16, all women)	UPSIT® + ODT	Very low weight patients with AN showed impairments in their ability to identify and detect odors
	Kopala et al[1036]	1995	3b	Observational, cross-sectional, case-control	Patients with AN (n = 27) Controls (n = 50, all women)	UPSIT®	No relevant difference in OF between the AN and control groups
	Smoliner et al[1026]	2013	4	Observational, cross-sectional, case-control	Cohort (n = 137 women/54 men) 4 patients had a BMI <20 kg/m^2	SS-ID (12 item)	No association between nutritional status and OD was found in geriatric patients
	Lombion-Pouthier et al[1037]	2005	4	Observational, cross-sectional, case-control	Patients with AN (n = 17) Controls (n = 58, all women)	Test Olfactif	Patients with AN had higher olfactory sensitivity compared with controls
	Roessner et al[1023]	2005	4	Observational, cross-sectional, case-control	Patients with AN (n = 17) Controls (n = 15, all women)	SS-TDI	Patients with AN had lower odor threshold and discrimination function compared with controls
	Schreder et al[1024]	2008	3b	Observational, cross-sectional, case-control	Patients with AN (n = 12) Controls (n = 24, all women)	SS-TDI	Patients with AN had lower overall OF compared with controls
	Aschenbrenn et al[1027]	2009	3b	Observational, cross-sectional, case-control	Patients with AN (n = 16) Controls (n = 23, all women)	SS-TDI	Overall OF was lower in patients with AN compared with controls

(Continues)

TABLE VII.16b (Continued)

Author	Year	LOE	Study design	Study groups	Olfactory test method used	Conclusions
Rapps et al[1028]	2010	3b	Observational, cross-sectional, case-control	Patients with AN (n = 19) Controls (n = 21, all women)	SS-TDI	Odor identification function was lower in patients with AN compared with controls
Schecklmann et al[1029]	2012	3b	Observational, cross-sectional, case-control	Patients with AN (n = 26) Controls (n = 23, all women)	SS-TDI	Odor identification function was higher in patients with AN compared with controls
Stein et al[1038]	2012	4	Observational, cross-sectional, case-control	Patients with AN-R (n = 40) Patients with AN-BP (n = 23) Controls (n = 20, all women)	Bottle threshold and discrimination test	Patients with AN had higher odor discrimination but lower threshold function compared with controls
Dazzi et al[1030]	2013	4	Observational, cross-sectional, case-control	Patients with AN (n = 18) Controls (n = 19, all women)	SS-TDI	Overall OF was higher in patients with AN compared with controls
Fernández -Aranda et al[1031*]	2016	3b	Observational, cross-sectional, case-control	Patients with AN (n = 64) Controls (n = 80, all women)	SS-TDI	Overall OF was higher in patients with AN compared with controls
Bentz et al[1032]	2017	3b	Observational, cross-sectional, case-control	Patients with AN, (n = 43) Controls (n = 39, all women)	SS-ID and T	Patients with AN had higher olfactory sensitivity compared with controls
Fernandez-Garcia et al[1033*]	2017	3b	Observational, cross-sectional, case-control	Patients with low weight (n = 17) Controls (n = 77, all women)	SS-TDI	No relevant difference in OF between the low weight and control groups
Tonacci et al[1034†]	2019	3b	Observational, cross-sectional, case-control	Patients with AN (n = 19) Controls (n = 19, all women)	SS-TDI extended	No relevant difference in OF between the AN and control groups
Kinnaird et al[1025]	2020	3b	Observational, cross-sectional, case-control	Patients with AN (n = 38 women/2 men) Controls (n = 38 women/2 men)	SS-TDI	No relevant difference in OF between the AN and control groups
Islam et al[1022]	2015	3a	Systematic review	14 studies		The findings indicate alterations of smell capacity in patients with AN
Mai et al[1021]	2020	1	Systematic review and meta-analysis	14 studies		Olfaction was largely intact in patients with AN compared with controls

AN = anorexia nervosa; BMI = body mass index; B-SIT = Brief Smell Identification Test; CCCRC = Connecticut Chemosensory Clinical Research Center; ETOC = European Test of Olfactory Capabilities; LOE = level of evidence; OD = olfactory dysnsfunction; ODT = odor detection threshold; OF = olfactory function; OLFACT = Olfactory Function Assessment by Computerized Testing; SS-ID = Sniffin' Sticks identification only; SS-T = Sniffin' Sticks threshold only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

with migraine when compared with healthy controls, with no difference in olfactory sulcus length.[978]

Fewer than 1% of migraine patients report olfactory hallucinations, which usually correlates with osmophobia and migraine severity.[979] 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 to 60 minutes, leading some to speculate it is a migraine aura.[980] More data are needed to determine the true extent of OD in patients with primary headache syndromes.

OD can be related to primary headache syndromes.

Aggregate grade of evidence: B (Level 1: one study; Level 3: three studies; Level 4: two studies).

M | Congenital

Unlike acquired smell loss, congenital smell loss is present at birth and may be either isolated or syndromic.[980] Isolated congenital anosmia (ICA) is a rare form of OD (0%–4%) and is a diagnosis of exclusion in nonsyndromic patients with no memory of smell, a history which may be difficult to accurately obtain.[980–983] Patients may seek care in childhood because of parental concerns but often do not present until adulthood.[984] While patients may occasionally have specific anosmia for particular odorants, one study showed a 93.1% rate of total anosmia in patients with ICA.[985,986]

ICA may be the result of sinonasal malformations impairing odorant transport to the olfactory neuroepithelium (eg, choanal atresia and OC maldevelopment), disrupted signal transduction, or pathology of cortical structures necessary for olfactory processing.[980] Characteristic MRI findings include underdevelopment of the OB or sulcus, an imperforate cribriform plate, and/or distinct changes in the volume of cortical regions associated with olfactory memory.[987–991] Biopsies may yield respiratory rather than OE findings.[992] Genetic factors likely play some role and family clusters have been identified with CNGA2 and TENMI1 mutations on whole exome sequencing.[993–996]

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.[997] Associations have been noted between anosmia and CHARGE syndrome, with CHD7 and other gene mutations identified on gene sequencing.[995,998] Congenital insensitivity to pain is associated with hyposmia through a SCN9A mutation.[999] Syndromic ciliopathies, such as Bardet-Biedl, have also been associated with congenital hyposmia from basic research on mechanisms[1000,1001] and by a matched-controlled study.[1002] Holoprosencephaly associated with absence of the entire olfactory apparatus leads to smell loss but often goes unnoticed.[980]

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 5000 to 10,000.[983] One retrospective analysis of clinical visits for confirmed smell loss in children revealed 67% with ICA.[982] 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 and found sinonasal and obstructive causes as more common, demonstrating the impact of patient selection and inclusion criteria on study results.[984,1003] A cross-sectional study found those with congenital anosmia had the worst thresholds among all causes, typically with no measurable OF.[984]

In regards to the evaluation and management of congenital anosmia, multiple studies have demonstrated the value of MRI with a relatively high rate of abnormalities identified.[1003–1006] The role of CT is less clear but may be helpful to evaluate choanal atresia or nasal cavity hypoplasia.[1006] Total anosmia, which is common to congenital anosmia, is associated with a worse prognosis for functional recovery. Olfactory ERPs can provide prognostic information in ICA.[1007] Treatment remains challenging, with 0% of patients with ICA in one series demonstrating improvement compared with 59.6% of postviral patients.[1008] 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.[1008,1009,1010] 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 to more accurately characterize and identify potential treatment options.

There are various congenital causes of smell loss.

Aggregate grade of evidence: C (Level 2: one study; Level 3: one study; Level 4: 15 studies).

N | Related to extremely high or low body mass index (BMI)

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

The literature evaluating the impact of extremely low body mass index (BMI) on OF included one meta-analysis,[1011] which concluded that OF is mainly intact in

TABLE VII.17 Section evidence summary: Related to smoking

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Dinc, et al[1071]	2020	Prospective-cohort, intervention	2	28 volunteers who were admitted to a smoking cessation section program and with chemosensory-related conditions Average of 22 cigarettesper day	SS-TDI extended, immediately before smoking cessation and 45 days after smoking cessation	Cigarettes per day and years smoking	Improvement in measured OF as soon as 45 days after smoking cessation, with more improvements in patients who had smoked for the fewest years before cessation
Ottaviano et al[1072]	2012	Prospective, randomized, double-blind	2	70 consecutive smokers (18 to 65 years) with a diagnosis of nonallergic CRS and a cigarette smoking habit for ≥5 years Nonallergic CRS, based on clinical evidence, nasal resistances, cytology, and olfactory thresholds	SS-T (butanol)	Cigarettes per day and years smoking	Simple, isotonic sodium chloride solution nasal irrigations significantly improved olfactory threshold
Danielides et al[1073]	2009	Prospective cohort	2	Smokers consisted of 22 men and 22 women (mean age = 46 years) who averaged 20 cigarettes per day Excluded were patients who were past smokers, normosmics (by testing), and those refusing to quit smoking after surgery	SS-TDI extended at baseline and 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 NPs presented a highly significant improvement in OF 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[1074]	2013	RCT	2	Adult daily smokers (n = 1126) and former smokers (n = 3239) Daily smokers were assigned randomly to continue smoking for 2 weeks or to stop smoking Occasional smokers and never-smokers were excluded	Self-reported smell and taste from "very poor" to "very good"	Revised Minnesota Withdrawal Scale Cigarettes per day and years smoking	Smokers who abstained from smoking reported improvements in the sense of smell right after quitting as well as improved sense of taste and sore throat

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TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Siegel et al.[1075]	2019	Population survey, case series	4	3528 older adults, including 1526 former smokers	SS-ID (5 odors)	Nonsmokers, former smokers (asking age started smoking regularly, age quit, number of cigarettes smoked on average per day), and current smokers (age started, number of cigarettes on average day)	Smoking-mediated OD is reversible but may persist for 15 years after smoking cessation Former smokers who had quit within 15 years had significantly impaired olfaction compared with never-smokers, but those who quit >15 years ago had similar olfaction as never-smokers
Schubert et al[1076]	2015	Prospective cohort	2	3296 participants (aged 21–84 years) in the baseline Beaver Dam Offspring Study (2005–2008), and 2792 (84.7%) of them, plus an additional 80 individuals who were unable to participate in the baseline phase	SDOIT	Current, former, or never-smoker	Current smoking (vs never-smoking) was associated with increased risk of olfactory decline
Hoffman et al[1077]	2016	US nationally representative, cross-sectional	4	1818 NHANES participants aged ≥40 years, 1281 (70.5 %) completed the examination	PST	Current, ever, and never-smoker	Smoking was not identified as a risk factor for OD; the logistic regression unexpectedly showed that past smoking, after adjusting for age and sex, was associated with decreased risk of OD
Pinto et al.[1078]	2014	Cross-sectional survey	4	n = 3005, with oversampled Black and Hispanic individuals, men, and oldest participants	SS-ID (5 odors)	Current smoking, based on either salivary cotinine level (n = 2219) or self-report (n = 709)	Smoking did not explain the worse OF found in Black and Hispanic participants, who had markedly worse OF (controlling for sex and age) compared with White participants In re-analysis of these data (Ajmani et al, 2017, see below), smoking did not associate significantly with the odds of OD

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Jalali et al[1079]	2020	Population-based cross-sectional	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	History of smoking, smoking dose (pack-years) A cigarette pack-year was defined as a pack of cigarettes (20 cigarettes) smoked every day for 1 year	OD frequency in smokers (22.5%) was significantly more frequent than in former (19.8%) and nonsmokers (13.2%) There was a significant negative association between total scores of Iran Smell Identification Task and the total number of cigarettes
Fluitman et al[1080]	2019	Cross-sectional analysis within a cohort	2	824 Dutch community-dwelling older adults from the ongoing Longitudinal Aging Study Amsterdam	UPSIT®	Smoking status was dichotomized into nonsmokers (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 vs 33, adjusted $P = 1.000$) No difference in the number of cigarettes smoked per week by categories of normosmic, microsmic and anosmic Lower OF scores were associated with lower BMI in older adults who smoke, but not in older adults who do not smoke
Khil et al[1081]	2015	Cross-sectional	2	Random sample of 3820 inhabitants aged 25 to 74 years from the population register of Dortmund, a city in western Germany	SS-ID (12 odors)	Smoking status (never-, former, current smoker)	Current smoking was significantly associated with greater odds of olfactory impairment
Schubert et al[1082]	2012	Population-based cross-sectional	2	2838 participants, 1293 (45.6%) men and 1545 (54.4%) women	SDOIT and related olfaction questions. "Do foods you eat now taste as good as when you were younger?" and "Do you experience food flavors (eg, chocolate, the same as you used to?"	Smoking history (ever-smoked ≥100 cigarettes), exposure to environmental tobacco smoke at home, work, and in social situations	History of smoking was associated with an increased odds of olfactory impairment in women only (ever-smoked vs never-smoked)

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Doty et al[1083]	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); 1131 elderly twins (513 men, 618 women)	B-SIT	Never, past, current	Smoking explained significant variability in odor identification ability in multiple regression analysis
Ranft et al[1084]	2009	Prospective cohort	2	402 older adults who lived at the same address for 20 years	SS-ID (16 odors)	Nonsmokers (n = 388); former smokers (15%); passive smoker (40%)	No effects of smoking on odor identification
Vennemann et al[1085]	2008	Cross-sectional population survey	2	1312 participants (randomly drawn) within 5-year age groups (25 to 75 years), stratified by sex	SS-ID (12 odors)	Current smoker, exsmoker, nonsmoker	Current smokers had a greater risk for smell impairment (adjusted 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[1086]	2002	Population-based cross-sectional	2	43 to 84 years (mean age, 69 years) in 1987–1988, residence of Bear Dam in 1987–1988, 2800 participants (did not exclude patients with dementia but less likely to participate in olfactory testing)	SDOIT and related olfaction questions "Do you have a normal sense of smell (compared with other people)?"	Current, former, never-smokers	Current vs never-smokers had 93% greater odds of OD
Veyseller et al[1087]	2014	Case-control	4	426 healthy volunteers without otolaryngologic conditions causing OD (measured or self-reported)	CCCRC olfactory test	Smokers vs nonsmokers	Smokers averaged significantly lower CCCRC scores (threshold, odor identification) than nonsmokers

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TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Liu et al[1088]	1995	Cross-sectional	4	510 participants (aged ≥50 years), 239 men and 271 women	B-SIT	Ever smoker, nonsmoker	Smoking status (ever) had independent effects on odor identification in multiple regression analysis
Mackay-Sim et al[1089]	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	SS-TDI	Smokers vs nonsmokers	No effects of smoking on OF, although most smokers were aged <40 years (suggesting less exposure to smoking)
Ishimaru et al[1090]	2007	Cross-sectional	2b	557 Japanese adults (368 men and 189 women)	B-SIT	Brinkman Index (number of cigarettes smoked per day multiplied by years of smoking) and urine test for nicotine intake level	Smokers and previous smokers had lower OF than nonsmokers
Frye et al[1091]	1990	Cross-sectional	2b	638 employees (553 men, 85 women; mean age, 43 years) of a large chemical manufacturing facility 260 never smokers 197 former smokers 170 current smokers	UPSIT®	Pack-years	Current smokers were nearly twice as likely to have an olfactory deficit than persons who never smoked (adjusted odds ratio) No elevated risk of OD 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[1092]	1984	Cross-sectional	2b	1339 volunteers (aged, 10 to 99 years) without reported smell abnormalities and who were able to correctly identify at least half of the odorants	UPSIT®	Smokers, nonsmokers	Current smoking was associated with lower odor identification ability, but the effects were not large and not in a dose relationship

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Delgado-Losada et al[1093]	2020	Cross-sectional	4	209 healthy normosmic volunteers (without any conditions associated with OD)	SS-TDI extended	Self-reported smokers vs nonsmokers	No differences in OD between smokers and nonsmokers
Nettore et al[1094]	2020	Cross-sectional	2b	348 participants (n = 241 women, 107 men), with a mean age of 42.41±15.63 years who did not report a smell or taste problem 25% of the sample smoked, averaging 10.52±8.20 cigarettes per day and for 15.15±12.77 years	Flavor identification task of 20 flavors Subjective chemosensory function, namely flavor ("How would you rate your fine taste, eg, during eating and drinking?") on a VAS	Nonsmokers (never smoked; smoking cessation >10 years previously) vs current (number of cigarettes per day, number of years smoking)	Cigarette smoking did not seem to influence flavor recognition Age and sex differences were seen
Duffy et al[1095]	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 smokers had measured OD, primarily hyposmia, which was up to 7-fold higher than the nonsmokers from 2013–2014 NHANES Awareness of the problem among those with measured dysfunction (sensitivity of self-report) was low
Katotomichelakis et al[1096]	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 no abnormal nose and the paranasal sinuses No history of any major olfactory disturbance	SS-TDI	Pack-years	Smokers had significantly lower function for olfactory identification, detection, and threshold, even after controlling for age and sex in multivariate regression and logistic analysis and treating pack-years as a continuous variable

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Cardesín et al[1097]	2006	Cross-sectional	4	120 healthy volunteers without subjective olfactory disturbances (January 2001 to February 2003)	BAST-24	Smokers vs nonsmokers	Smokers scored lower on odor identification for some odors
Glennon et al[1098]	2019	Cross-sectional	2	Adults aged ≥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-ratings based on a score of three questions (olfactory problems in the past years; worse ability since age 25; phantom smells)	Self-reported by chronicity (pack-years) and dependency (time to first cigarette on waking) and verified by serum cotinine Smoking (never, former, current)	Estimated prevalence of 22.3% in altered olfaction was with age-related increases ≥10 pack-year smokers had significantly greater odds of altered olfaction vs never-smokers Greater odds among current smokers (≥10 pack-years) who also had high nicotine dependence (smoked within ≤30 minutes of waking) Light smokers (≤10 pack-year smokers) did not show increased odds vs never-smokers Current smokers who also were heavy drinkers (≥4 drinks per day) had the highest odds for altered olfaction (odds ratio, 1.96; confidence interval, 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[1099]	2016	Cross-sectional	4	3603 adults, aged ≥40 years, who answered the Chemosensory Questionnaire (response rate 99.9%)	NHANES self-ratings 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 (packs of cigarettes smoked per day × years smoked), and ≥10 pack-years	Logistic regression, ≥10 pack-years was not a significant predictor of self-reported smell alteration in adjusted logistic regression models

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Lee et al[1100]	2015	Cross-sectional	4	1589 adults completed questionnaires on rhinologic symptoms and smoking behaviors and underwent nasal endoscopy CRS diagnosis from ≥2 symptoms, including OD	"Have you had problems with your sense of smell during the past 3 months?"	Active smokers, passive smokers, and nonsmokers based on questionnaire responses and urine cotinine levels	The odds of self-reported OD did not vary significantly in active smokers vs passive or nonsmokers in adjusted logistic regression (in younger ≥19 years or older ≥40 years) Total smoking period (years) was significantly associated with CRS, but not other smoking behaviors (age started, number of cigarettes per day, pack-years of smoking
Huang et al[1101]	2017	Cross-sectional	4	12,627 Chinese participants (10,418 men and 2209 women; mean age, 54.4 years) 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 are supposed to for ≥3 months?"	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 chemosensory dysfunction and a higher concentration of total cholesterol, particularly among younger adults and nonsmokers
Collins et al[1102]	1999	Cross-sectional	2	144 volunteers, including 60 smokers (22 men, 27 women), 61 nonsmokers (19 men, 42 women), and 23 passive smokers (5 men, 18 women)	Self-reported "Has your sense of smell become reduced?" on VAS	Smoker, nonsmoker, passive smoker, nonsmoker (never, not smoking >5 years)	Smokers were four times and passive smokers six times more likely to report a diminished sense of smell than nonsmokers
Fjaeldstad et al[1103]	2021	Retrospect observational	4	3900 patients with olfactory loss; 521 patients were current smokers and 316 patients had a history of smoking	SS-TDI extended	Smoking dose was calculated in pack-years (packs smoked per day × with number of years where smoking occurred)	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

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Erdem et al[1104]	2019	Prospective, preoperative and postoperative study	2b	60 patients post-CABG (first time) divided into 30 off-pump and 30 on-pump CABG groups	SIT	Smoking: yes/no	Smokers had lower OF preoperatively and postoperatively
Sharer et al[1105]	2015	Case-control analysis	4	323 patients with PD and 323 controls closely matched individually on age, sex, and smoking history (never, past, or current)	UPSIT®	Never-, past, current smoker	In controls, smokers had significantly lower odor idenitification scores; current PD smokers had higher odor identification scores than former or never-smokers
Siderowf et al[1106]	2007	Observational	4	173 first-degree relatives (aged >50 years, within 10 years of the age of PD onset), free of conditions that could affect OF; excluded current smokers	UPSIT®	Never smokers (1 to 10 lifetime pack-years) and >10 pack-years	Nonsignificant association between former smoking status and olfactory performance
Mori et al[1107]	2013	Multicenter prospective cohort study	2b	418 patients with preoperative olfactory data by ECRS or NECRS	T&T olfactometer and intravenous olfactory test (garlic odor)	Past, current, nonsmokers	Current smoking was a risk factor for ECRS OD was more severe and more prevalent in patients with ECRS than in patients with NECRS
Litvack et al[1108]	2008	Multiinstitutional cross-sectional analysis	2b	396 participants with a diagnosis of CRS recruited from three tertiary care centers over a 3-year period	UPSIT®	Current tobacco use	Current smokers were at increased odds of anosmia as compared with patients <65 years, without nasal polyposis, nonasthmatics, and nonsmokers
Sugiyama et al[1109]	2002	Case series	4	37 patients (30 men, 7 women; mean age, 43 years) who underwent functional ESS 13 (35.1 %) were cigarette smokers; 18 had undergone previous surgical intervention for their nasal disease	UPSIT®	Pack-years	Significant correlation between greater pack-years and lower postoperative OF in a population with high levels of smoking

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Şanlı et al[1110]	2016	Case series	4	1840 randomly selected patients (823 men, 1017 women), aged >25 years, admitted to an ear, nose, and throat outpatient clinic over 1 month (March 2014)	Self-reported "taste" disorders and smell disorders	Smokers (≥10 cigarettes per day for ≥5 years, n = 514) Exsmokers (no smoking for ≥1 year after ≥5 years of smoking, n = 268) Never-smokers (n = 1058) 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 similar in the control group All symptoms were found to be significantly lower in exsmokers
Pepino et al[1111]	2014	Case-control	4	14 obese smokers, 11 obese never-smokers, 10 normal-weight smokers, 12 normal-weight never-smokers	Retronsal 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 per day, age smoking started, and 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[1112]	2014	Case-control	4	24 smokers and 24 participants who had never consumed tobacco, matched for sex and age Smokers were under outpatient pulmonary care	Smell diskettes odor identification task	Current smokers	Odor identification score averaged lower in smokers vs nonsmokers related to muscle compensation during swallowing
Schriever et al[1113]	2013	Case-control	4	21 smokers (9 men, 12 women; mean age, 22.5 years) and 59 nonsmoking controls (23 men, 26 women; mean age, 23.9 years) matched for sex and age	PEA threshold	Smokers ≥3 cigarettes per day for an average duration of smoking of 7.5 years Former 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	Average threshold for PEA did not differ by smoking status; odor ID trended to be lower in smokers. Smokers had significantly lower OBV than did nonsmokers. There was no significant correlation of duration of smoking with OBV. Uncertain if quitting smoking reverses association OBV differences.

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Hayes et al[1114]	2012	Case-control	4	23 nonsmokers (10 men and 13 women; mean age, 25 years) and 23 smokers (11 men and 12 women; mean age, 24 years) Smokers averaged 8 cigarettes per day for an average of 5 years or 2.4 pack-years Nonsmokers did not have second-hand smoke exposure or were former smokers	n-butanol and PEA thresholds	Pack-years (amount, years)	Smokers had higher olfactory detection thresholds, including greater pack-years and higher thresholds
Rosenblatt et al[1115]	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 past 10 years) Ten patients were nonsmokers Smoking status was confirmed by end-expired carbon monoxide	Current smokers had higher olfactory threshold that was reduced with an experimental abstinence
Ahlström et al[1116]	1987	Case-control	4	67 adults (32 men, 35 women; aged 19 to 43 years)—26 smokers (14 men, 12 women), 26 nonsmokers (13 men, 13 women), 15 passive smokers (5 men, 10 women)	Six concentrations (pyridine and n-butanol) from perceptually weak to moderately strong odors	Smokers, nonsmokers, passive smoke exposure	Smokers reported lower intensities than nonsmokers, among all concentrations
Cometto-Muñiz et al[1117]	1982	Case-control	4	21 smokers (7 men, 14 women; average age, 25 years), with an average daily consumption of 15 cigarettes for 9 years 20 nonsmokers (6 men, 14 women; average age, 25.1 years)	Perceived intensity (magnitude matching) of irritation, odorant, and tone	Smokers vs nonsmokers	Smokers perceived nasally inhaled common chemical stimuli less keenly than nonsmokers Short periods of smoking further impaired the smoker's sensitivity to an irritant The odor intensity was not different, rather the pungency

(Continues)

TABLE VII.17 (Continued)

Author	Year	Design	LOE	Study groups	Olfactory indicator	Smoking measure	Conclusions
Ajmani et al[1070]	2017	Meta-analysis of observational studies between 1970 and 2015	1	7 studies included 11,771 participants (highlighted in orange above)	Odor identification	Current, former, never	Pooled analysis showed that smoking was associated with a 59% increased odds of OD Significantly increased odds of OD was not seen in former smokers than never-smokers

BAST-24 = Barcelona Smell Test-24; B-SIT = Brief Smell Identification Test; CABG = coronary artery bypass grafting; CCCRC = Connecticut Chemosensory Clinical Research Center; CRS = chronic rhinosinusitis; CT = computed tomography; ECRS = eosinophilic chronic rhinosinusitis; ESS = endoscopic sinus surgery; LOE = level of evidence; NECRS = noneosinophilic chronic rhinosinusitis; NHANES = National Health and Nutrition Examination Survey; NP = nasal polyp; OD = olfactory function; OF = olfactory function; PD = Parkinson disease; PEA = phenylethyl alcohol; PST = Pocket Smell Test; RCT = randomized controlled trial; SDOIT = San Diego Odor Identification Test; SIT = Smell Identification Test; SS-ID = Sniffin' Sticks identification only; SS-T = Sniffin' Sticks threshold only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

patients with AN. One systematic review concluded that there might be alterations of OF in patients with AN.[1012] The current review summarizes all studies that measured OF in patients with extremely low BMI.

Most studies utilized the SS threshold, discrimination, identification combination (SS-TDI) test.[1013–1024] While older studies showed significant heterogeneity of reported results and conclusions,[1013,1014,1016–1019,1025–1028] three recently published studies[1015,1023,1024] provided further evidence that there might exist no relevant differences in OF between patients with AN and controls. Furthermore, those studies that concluded significant differences between patients with AN and controls only showed marginal differences.[1013,1014,1017–1022,1025,1027,1028]

The literature evaluating the impact of extremely high BMI on OF included one systematic review that concluded solid evidence for a negative correlation between individual body weight and OF.[1029] The current review summarizes all studies that measured OF in patients with extremely high BMI.

Most studies utilized the SS-TDI test.[1030–1035] Eight studies showed greater OD risk among obese patients.[1030,1031,1035–1040] Five studies showed no relevant association between extremely high BMI and OD.[1034,1041–1044] One study showed an age-dependent association between BMI and OF,[1045] and the remaining two studies reported better OF in morbid obesity.[1046,1047]

One cross-sectional study revealed a positive correlation between correctly identified odors and BMI,[1048] while the longitudinal study revealed no relevant association between BMI and OF.[1049]

Two cross-sectional studies reported a higher OD risk for morbidly obese patients.[1050,1051] Five interventional studies showed that OF improved significantly after bariatric surgery.[1052–1057] Two studies showed no effect of bariatric surgery on OF.[1058,1059]

Extremely low body weight is not associated with increased OD risk

Aggregate grade of evidence: B (Level 3: one study; Level 3b: 10 studies; Level 4: six studies).

Extremely high body weight increases OD risk. Weight loss might reverse obesity-related OD.

Aggregate grade of evidence: B (Level 2: one study; Level 3b: 14 studies; Level 4: 12 studies; Level 5: one study).

O | Related to smoking

Chronic cigarette smoking may contribute to OD. Literature evaluating chronic smoking on OF includes a meta-analysis, concluding that current (but not necessarily former) smoking was associated with 59% greater OD risk.[1060] Additional studies are reviewed below and in Table VII.17.

All interventional studies with measured olfaction show OF improvement with smoking cessation, nasal irrigation, and NP surgery for smokers with postsurgery smoking cessation.[1061–1064]

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.[1065,1066]

One 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.[1067,1068]

Nine population-based studies showed greater OD risk among smokers, and two did not.[1069–1079] Of community-based studies, six studies showed greater OD risk among smokers, with one demonstrating dose-response relationships. Two only studies included

TABLE VII.18 Section evidence summary: Idiopathic

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Rombaux et al[1127]	2010	4	Case-control	Idiopathic olfactory loss Matched controls	SS-TDI MRI brain findings	OBV smaller in patients with idiopathic loss compared with controls OBV correlates with threshold scores
Fonteyn et al[1118]	2014	4	Case series	Heterogenous population with diverse olfactory loss etiology	Orthonasal SS-TDI Retronasal psychophysical olfatory testing (powder application)	IOD represented 16.3% of diverse olfactory loss Orthonasal and retronasal testing scores were statistically correlated in patients with IOD
Hoekman et al[1120]	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[1125]	2014	4	Case-control	Idiopathic olfactory loss Matched controls	SS-TDI and T&T olfactometer MRI brain findings	Decreased gray matter volume in primary and secondary olfactory centers of the brain in patients with idiopathic loss compared with controls
Hald et al[1119]	2020	4	Case series	IOD Sinonasal OD PIOD	SS-TDI extended Gustatory testing (taste drop and spray tests) Neurologic and psychiatric screening (MMSE, Major Depression Inventory)	No difference in neurologic and psychiatric screening between groups IOD represented 30% of the patient population
Liu et al[1128]	2018	4	Case-control	IOD Matched controls	SS-TDI and T&T olfactometer Electrophysiologic testing (electroencephalography, ERP) MRI brain findings	Decreased amplitude of olfactory ERP in patients with IOD compared with controls OBV smaller in patients with idiopathic loss compared with controls

ERP = event-related potential; IOD = idiopathic olfactory dysfunction; LOE = level of evidence; MMSE = Mini-Mental Status Examination; MRI = magnetic resonance imaging; OBV = olfactory bulb volume; PIOD = postinfectious olfactory dysfunction; OD = olfactory dysfunction; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi.

participants who denied OD or OD-associated problems and failed to find significant smoking-OD risk associations.[1080–1087]

When looking at cross-sectional studies with self-rated olfaction, a larger US data set revealed significant smoking-OD associations, partially mediated by olfactory-related conditions. In Korean adults with CRS, smoking was associated with CRS but not OD.[1088–1090] Another nonrepresentative population-based study showed no significant smoking-OD associations,[1091] but a community-based study showed significant smoking-OD associations.[1092]

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 posttraumatic OD (PTOD).[1093–1099]

Two perioperative studies in the context of postcoronary artery bypass graft and postendoscopy sinus surgery found

smoking to be associated with postoperative OD.[1094,1063] In two studies, smokers with CRS had greater risk of OD, particularly those with eosinophilic CRS.[1097,1098]

When evaluating patients with PD, a case-control analysis found greater overall risk of OD in smokers compared with nonsmokers but lower relative risk in smokers with PD. In another study, first-degree nonsmoker relatives of patients with PD showed nonsignificant smoking-OD risk associations.[1095,1096]

One observational study of patients seen in an ear, nose, and throat outpatient clinic reported that smokers had a higher risk of OD.[1100]

Two studies found worse OF in smokers (versus nonsmokers): 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,while another reported lower OBV in smokers. In addition, one study reported better OF with brief (16- to 20-hour) abstinence from smoking.[1101–48]

Chronic cigarette smoking increases the risk of OD. Former smokers may recover OF, although the length of smoking may influence recovery.

Aggregate grade of evidence: B (Level 1: one study; Level 2: 21 studies; Level 3: one study; Level 4: 24 studies).

P | Idiopathic

Idiopathic OD (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 OD.[1106–1108] It is possible that IOD may represent an early manifestation of neurodegenerative disease in a select group of patients. For instance, Haehner et al[1109] found that 10% of patients who were diagnosed with IOD ultimately developed PD 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 CNS and olfactory pathways are potentially implicated in the pathogenesis of IOD. Several studies have shown that olfactory performance correlates with cortical volume of the OFC and insular cortex in healthy adults.[1110,1111] Moreover, these portions of the brain decline in volume in patients with diverse causes of OD.[1112] Yao et al[1113] showed that in a population of patients with IOD, significant grey matter volume decline was seen in the POC and secondary olfactory areas (OFC, insular cortex, anterior cingulate cortex, and parahippocampal cortex). OBV changes are common in many causes of OD, including patients with IOD, and are thought to represent a declining population of olfactory neurons secondary to decreased olfactory signal transduction from the neuroepithelium.[1114–1116] Despite the concordance of these findings in patients with IOD, there are conflicting reports that fail to demonstrate identifiable radiologic irregularities.[1108] Moreover, it is unknown whether structural changes in the brain are a consequence of the pathophysiologic mechanism of IOD, or, rather, a secondary manifestation of diminished OF.

Beyond radiologic findings, patients with IOD may have alteration in olfactory signal transduction. Liu et al[1116] compared the amplitude and latency of chemosensory ERPs in patients with IOD and normal healthy controls. In patients with IOD, a significant decrease in amplitude of ERPs likely represented either decreased populations of peripheral olfactory neurons or alterations in central olfactory pathways.

The current body of literature implicates CNS 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 causes.

A significant portion of patients with olfactory loss are placed into an idiopathic category, with likely multiple different causes leading to this diagnosis. More research is needed to better elucidate and therefore treat the underlying mechanisms.

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

VIII | EVALUATION AND DIAGNOSIS

A | History and physical examination

History and physical examinations are essential parts of the evaluation of patients with OD.[1118–1126] A thorough history provides a diagnosis of OD 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 causes among patients presenting with OD (Table VIII-1).[1118–1122,1125,1126] There were no randomized studies investigating the utility of history-taking or physical examination on the diagnosis of OD. Lack of higher-level evidence is expected given that history and physical examinations are essential to any medical diagnosis.

Clinical assessment of patients with OD should include general clinical history and specific questions related to

TABLE VIII.1 Section evidence summary: History and physical examination to guide diagnosis

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Deems[1129]	1991	4	Case series	Objective olfactory and gustatory dysfunction (n = 750)	History, physical examination, UPSIT®, PEA threshold	History and physical examination were used to delineate potential causes of OD
Temmel et al[1130]	2002	4	Case series	Objective hyposmia or anosmia (n = 278)	History, physical examination, SS-TDI	History and physical examination were used to delineate potential causes of OD
Landis et al[1131]	2004	4	Prospective cohort study	All patients seen in a tertiary center clinic (n = 1240)	History, physical examination, SS-TDI	History and physical examination were used to delineate potential causes of OD
Frasnelli et al[1132]	2004	4	Case report	Selected cases of OD (n = 5)	History, physical examination, SS-TDI	OD presented in various qualities and associated symptoms
Harris et al[1133]	2006	4	Case series	Subjective olfactory or gustatory dysfunction (n = 1000)	History, physical examination, butanol threshold, 10-odor identification test	History and physical examination were used to delineate potential causes of OD
Hummel et al[1134]	2017	5	Guideline	N	Recommendations on diagnosis and management of OD	History and full head and neck examination with endoscopy are recommended for patients with suspected olfactory loss Basic neurological examination is recommended for patients with potential underlying neurological etiology, although formal neurocognitive testing can be deferred to the specialist
Miwa et al[1135]	2019	5	Guideline	NA	Recommendations on management of OD	Various management options are available for patients presenting with OD by etiology
Seiden and Duncan[1136]	2001	4	Case series	Subjective OD (n = 428)	History, physical examination, UPSIT®	History and physical examination were used to delineate potential causes of OD Anterior rhinoscopy failed to diagnose conductive pathology in 51% of cases in comparison to 9% with nasal endoscopy

LOE = level of evidence; NA = not available; OD = olfactory dysfunction; PEA = phenylethyl alcohol; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

olfactory disorders. Several guidelines and multiple expert opinions suggest that the clinical history include the quality of olfactory changes, timing of onset, duration, associated factors, and social and family history.[1123,1124,1127,1128] History of OD 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 before 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.[1118,1122] Patients with OD frequently confuse symptoms of flavor loss resulting from the smell disturbance with true taste dysfunction.[1118] Further clarification on whether patients have primary gustatory dysfunction or taste alteration attributable 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 OD can be obtained from a history. Specifically, clinicians should obtain detailed history on sinonasal symptoms, infections, or traumatic events preceding the onset of OD, as these causes represent more than two thirds of patients presenting with OD. Sinonasal factors to ask about include previous URI, sinusitis, allergy, nasal obstruction, and epistaxis.[1129,1130] OD during an acute URI or sinusitis can initially represent as conductive loss, but persistent dysfunction after resolution of infectious symptoms may indicate sensorineural injury to the OE.[1119,1122] History of previous head trauma, nose/sinus surgeries, head and neck cancer, and radiation is important in determining the etiology of OD.[1131,1132] 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.[1118,1119,1122,1133] 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.[1134,1135]

Social history includes history of occupational and environmental exposure to toxins and substance use (ie, alcohol, smoking, cocaine, and other inhalants).[1136,1137] 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).[1118] Tobacco smoking history along with other substance use should be obtained in the assessment of OD.[1136]

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.[1138–1141] About 50% to 90% of patients diagnosed with AD or PD are affected by smell loss.[1138,1140–1143] OD has been identified as one of the early manifestations of the neurodegenerative diseases more commonly presenting with gradual onset hyposmia without obstructive symptoms.[1144–1146] Family history of neurodegenerative diseases and a complete medication list need to be additionally reviewed.

Physical examination includes a full head and neck examination followed by nasal endoscopy, otoscopy, and neurological examination including cranial nerve examination.[1118–1123,1125] 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, the OC and middle meatus should be carefully evaluated to rule out obstructive causes.[1123,1147] Validated clinical scoring systems such as the Lund-Kennedy scoring system[1148] or the Olfactory Cleft Endoscopy Scale[1149] 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[1125] found that OD with obstructive etiology was successfully diagnosed in 91% of cases with nasal endoscopy in comparison to 49% with anterior rhinoscopy. Use of intranasal anesthesia before nasal endoscopy may affect chemosensory test results and the clinical history itself. Welge-Lussen et al[1126] demonstrated that application of intranasal anesthesia reduces self-assessment of olfaction and odor discrimination among healthy volunteers.[1126] Therefore, chemosensory testing and obtaining the complete history should be performed before 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.[1150] 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 examination can be considered if dementia or other neurodegenerative disorders are suspected.[1123] Appropriate referral to specialists should be considered if either neurologic or neurotologic causes are suspected.

A complete history and physical examination, including nasal endoscopy, allows for appropriate diagnosis and management of OD.

Aggregate grade of evidence: C (Level 4: six studies; Level 5: two studies).

Benefit: Complete history and physical examination, with nasal endoscopy, guides the choice of appropriate diagnostic tests, helps avoid misdiagnosis, improves diagnostic accuracy, ensures that treatment is consistent with diagnosis, and guides patient expectations.

Harm: Minimal discomfort during physical examination and nasal endoscopy.

Cost: Minimal, although the cost of a doctor's visit is dependent on the health care system.

Benefits-harm assessment: Preponderance of benefit over harm.

Value judgments: None.

Policy level: Strong recommendation.

Intervention: History-taking and basic physical examination are essential in the diagnosis of OD. 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.

B | Imaging

Classic workup of patients with OD relies on thorough medical history, clinical examination, and evaluation of OF. This workup 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 CNS disease processes including tumors, and to counsel patients regarding overall prognosis.

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

1 | CT of the paranasal sinuses

There are four studies evaluating the usefulness of CT of the paranasal sinuses in patients with OD (Table VIII.2). All of these studies use noncontrast CT, viewed on bone window.

Three studies (two case series and one prospective cohort study) found that CT was useful in identifying OC obstruction, in the context of obstructive OD,[1150] COVID-19–related OD,[1151] and OC syndrome.[1152] One retrospective study evaluated the usefulness of CT scan to diagnose OD resulting from sinonasal disease (SND), in comparison to clinical examination.[1153] This study found that CT could be useful in refining the diagnosis since it was able to both diagnose SND in 7% of patients with suspected non-SND causes, as well as rule out SND in one third of patients with suspected SND, who then had normal CT imaging findings. Specifically, they found that 3% of patients with PIOD, 14% with PTOD, and 11% with IOD had signs of sinonasal inflammation. The authors therefore propose that CT scans are useful in patients with suspected non-SND OD 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 OF. Although CT imaging could provide 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 before CT imaging, according to available guidelines.[1154] CT scan (or other imaging, such as MRI) should be considered if the patient has unilateral pathology or suspicion of tumor or after failure of appropriate medical treatment. If tumor or malignancy is suspected, medical and imaging workup should be completed expeditiously.

CT imaging for the evaluation and diagnosis of OD

Aggregate grade of evidence: D (Level 3: one study; Level 4: three studies).

Benefit: Potential identification of treatable obstruction of the OC 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 LOE.

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 from a clearly attributable cause (postinfectious or posttraumatic) remains unanswered and no recommendation can be made. In PTOD, CT scan can be considered for identifying bony sequalae (septal fracture, fracture to the cribriform plate) or when a CSF leak is suspected. When OD is suspected to be from sinonasal inflammatory causes, a CT scan is helpful in its confirmation.

Policy level: Option.

Intervention: In case of suspected OC syndrome or sinonasal disease causing OD, 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 OD.

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; eight case series; 12 retrospective studies).

TABLE VIII.2 Sinus CT

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Yildirim et al[1163]	2020	3	Prospective cohort	106 patients with OD (41 postinfectious, 13 posttraumatic, 28 idiopathic, and 17 obstructive) 17 normosmic controls	Anterior cranial fossa fractures (CT) Aeration of the OC (CT) SS-TDI MRI of olfactory pathways	The obstructive group was characterized by loss of aeration of the OC
Kandemirli et al[1164]	2020	4	Prospective case series	23 patients with persistent COVID-19–related OD	SS-TDI OC aeration pattern (CT) MRI of olfactory pathways	OC opacification was seen in 73.9% of cases
Mueller et al[1166]	2006	4	Retrospective	137 patients with OD	SS-TDI CT scan of the paranasal sinuses Assumed diagnosis (sinonasal disease related or not) vs CT-based diagnosis	CT-diagnosed sinonasal disease in 7% patients suspected of nonsinonasal disease One third of patients with suspected sinonasal disease before imaging had normal CT
Biacabe et al[1165]	2004	4	Retrospective case series	13 patients with OC disease	Olfactory threshold test Endoscopic evaluation CT scan of the paranasal sinuses	CT scan provided useful information for diagnosing OC syndrome

CT = computed tomography; LOE = level of evidence; MRI = magnetic resonance imaging; OC = olfactory cleft; OD = olfactory dysfunction; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination.

As a major relay of the olfactory pathways, the most studied structure is the 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 (nine prospective cohort studies, six case series, and six retrospective studies) agree that OBV is decreased in patients experiencing a wide range of pathologies affecting OF.[1150,1151,1155,1156,1158–1160,1162,1164,1165,1168,1171,1174,1177–1184] Indeed, patients with posttraumatic,[1164,1170,1181] postinfectious,[1156,1164] idiopathic,[1150,1155,1160] obstructive,[1150] and congenital[1165,1174] OD were found to have smaller OBVs compared with normosmic controls.

Several studies (two prospective cohort studies, three case series, and four retrospective studies) have also found a positive correlation between OBV and OF,[1160,1164,1172,1176–1179,1183] notably in postinfectious,[1164,1177,1179] posttraumatic,[1164,1178,1181,1183] and idiopathic[1160] OD. However, some studies (one prospective cohort study, one case series) found no correlation between OBV and OF.[1162,1167] In the same vein, it has been described (one prospective cohort study, one retrospective study) that OBV correlates to the results of olfactory ERPs.[1162,1171] Qualitative OD also seems to be associated with OB reduction, since three studies (one prospective cohort study, two retrospective studies) have found that patients with parosmia have smaller OBVs.[1164,1178,1179]

Structural MRI studies have also investigated the plasticity of the OB over time. One prospective cohort study found that OBV is inversely correlated to the duration of the olfactory loss.[1156] Another prospective cohort study showed that changes in OF over time is correlated to change in OBV.[1163]

Three studies (one case series, two retrospective studies) have assessed the prognostic value of the OB. Some authors have found that the OBV and integrity are prognostic factors of recovery in postinfectious[1176] and posttraumatic[1166,1176] olfactory loss. In contrast, others found that the OBV was not an indicator of the prognosis of recovery[1169] in patients with IOD.

Another anatomical structure that has been widely investigated is the olfactory sulcus. Olfactory sulcus depth was reported (three prospective cohort studies, one retrospective study) to be smaller in patients with OD from various origins (postinfectious,[1150] posttraumatic,[1150] idiopathic,[1150] congenital[1158,1159,1165,1174]), while other studies found no difference in IOD[1155,1160] (two prospective cohort studies) or PTOD[1167] (one case series). It was also reported in one retrospective study that olfactory sulcus depth was correlated with OF in patients with all causes of OD.[1172]

It also appears from MRI studies that some causes have characteristic imaging features, rendering MRI useful to confirm the etiology of OD. Indeed, it was reliably found that patients with congenital anosmia have a severely hypoplastic or aplastic OB, and a shallow

TABLE VIII.3 MRI

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Yildirim et al[1163]	2020	3	Prospective cohort study	106 patients with OD (41 postinfectious, 13 posttraumatic, 28 idiopathic, and 17 obstructive) 17 normosmic controls	Morphology of the OB and olfactory nerve OBV SS-TDI CT of the anterior cranial fossa and OC	OBV was decreased in the idiopathic and obstructive groups compared with controls OS was smaller in all groups of OD OB had morphological particularities in postinfectious and idiopathic cases Frontobasal lesions were present in posttraumatic cases
Liu et al[1168]	2018	3	Prospective cohort	20 patients with IOD 20 normosmic controls	T&T olfactometer scores Chemosensory ERP OBV and OS depth	Patients with IOD had significantly smaller OBVs No difference was found in OS depth
Yao et al[1169]	2018	3	Prospective cohort	19 patients with PIOD 19 normosmic controls	T&T olfactometer scores OBV Voxel-based morphometry Time since injury	PIOD was associated to decreased OBV Duration of olfactory loss was negatively correlated with OBV
Lötsch et al[1170]	2015	3	Prospective cohort	41 patients with PTOD 23 patients with non-PTOD	SS-TDI Damages in 11 olfactory-relevant brain areas Development of an olfactory diagnostic algorithm	Lesions in OB, olfactory tract, and temporal lobe pole were able to predict posttraumatic anosmia with a high accuracy
Ottaviano et al[1171]	2015	3	Prospective cohort	38 patients with Kallmann syndrome 21 normosmic controls	SS-ID (12 odors) OB, olfactory tract, and OS morphology	Patients with Kallmann syndrome had significantly reduced OBV and OS depth Thicker cortex in the region close to OS OF correlated with OBV and cortical thickness
Huart et al[1172]	2012	3	Prospective cohort	36 patients with congenital anosmia 70 normosmic controls	Depth of the OS	Patients with congenital anosmia had smaller OS depth OS ≤8 mm clearly indicated congenital anosmia with a specificity of 1
Rombaux et al[1173]	2010	3	Prospective cohort	22 patients with IOD 22 normosmic controls	SS-TDI OBV and OS depth	OBV was smaller in IOD OS depth showed no difference Odor thresholds correlated with OBV

(Continues)

TABLE VIII.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Altighechi et al[1174]	2009	3	Prospective cohort	21 patients with PTOD 19 patients without PTOD 63 normosmic controls	OF CCCRC ID MRI: OB morphology, brain lesions SPECT: brain perfusion	Posttraumatic anosmics exhibited damage to the frontal lobes and OB
Goektas et al[1175]	2009	3	Prospective cohort	10 patients with PIOD 5 patients with PTOD 9 patients with IOD	SS-TDI Chemosensory ERPs OBV	Association between OBV and presence of olfactory ERPs No correlation between OBV and TDI score
Haehner et al[1176]	2008	3	Prospective before-after trial	20 patients with olfactory loss	SS-TDI at baseline and follow-up OBV at baseline and follow-up	OBV changes correlated with odor threshold changes
Mueller et al[1177]	2005	3	Prospective cohort study	22 patients with PIOD 9 patients with PTOD 17 normosmic controls	SS-TDI OBV	OBs were smaller in patients with OD compared with controls OBV correlated with OF OBs were smaller in patients with parosmia
Abolmaali et al[1178]	2002	3	Prospective cohort	16 patients with congenital anosmia 8 normosmic controls	Assessment of frontobasal structures	Patients with congenital anosmia had aplastic or hypoplastic OB OS depth reflected the presence of olfactory tract
Kandemirli et al[1164]	2020	4	Case series	23 patients with persistent COVID-19–related OD	SS-TDI OBV and quality and OS depth CT of the OC	OB abnormalities were seen (hypoplastic, 43%; signal abnormalities, 91.3%) POC showed signal abnormalities in 21% cases
AbdelBari et al[1179]	2020	4	Retrospective	70 patients with PTOD	OB integrity OF SS-TDI	OB integrity was a prognosis factor for olfactory recovery
Langdon et al[1180]	2018	4*	Prospective randomized controlled	42 patients with traumatic brain injury–induced OD	OF (VAS, BAST-24, n-butanol thresholds) MRI traumatic lesion score	OF was significantly associated with the overall MRI score, but not with the OBV or OS length
Chung et al[1181]	2018	4	Retrospective case series	34 patients with OD	Korean SS-TDI Questionnaires (SNOT-22, QOD) OBV and signal	OB atrophy was significantly higher in patients with anosmia/hyposmia vs those with normosmia No difference in OB signal between groups

(Continues)

TABLE VIII.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Shiga et al[1182]	2017	4	Retrospective case series	24 patients with IOD	T&T olfactometer at baseline and after treatment with Japanese herbal medicine OBV at baseline Olfacto-scintigraphy (nasal thallium administration and SPECT-CT) at baseline Prognosis of recovery	OBV was not an indicator of the prognosis of recovery
Lötsch et al[1183]	2016	4	Retrospective	143 patients with PTOD	SS-TDI Brain lesions pattern analysis	Higher prevalence of parosmia and tendency to phantosmia in patients with medium overall brain damage Lower frequency of lesions in the right temporal lobe in patients with parosmia Lesions of the right OB were more frequent in patients with anosmia Higher frequency of left frontal lobe lesions in patients with phantosmia
Miao et al[1184]	2015	4	Retrospective cohort	26 patients with PTOD 21 normosmic controls	T&T olfactometer Chemosensory ERPs OBV, OS depth, brain lesions	OBV was decreased in patients with PTOD Lesions at the level of the OB, olfactory tract, and gyrus rectus were associated with the results of the olfactory ERPs
Hummel et al[1185]	2015	4	Retrospective case series	378 patients with OD	SS-TDI OBV, OS depth	Correlation between OBV and OF Right OS correlated with OF OS was negatively correlated with age
Hoekman et al[1186]	2014	4	Retrospective case series	247 patients with IOD (130 scanned using MRI)	UPSIT® MRI findings Cost-effectiveness	Abnormalities were identified in 4.6% 0.8% of patients had olfactory loss attributable to imaging findings The estimated cost per attributable abnormal finding was $325,000 USD

(Continues)

TABLE VIII.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Levy et al[1187]	2013	4	Retrospective cohort	40 patients with isolated congenital anosmia 22 normosmic controls	OF (detection and recognition) OB, OS olfactory groove, and hippocampal morphology	Patients with congenital anosmia may show aplastic or hypoplastic OB, decreased OS depths, and/or abnormalities in hippocampal anatomy
Atighechi et al[1188]	2013	4	Retrospective case series	63 patients with PTOD	CCCRC olfactory test MRI: abnormalities of the OB, olfactory tract, and frontal and temporal lobes SPECT: perfusion in the frontal and temporal lobes	MRI and SPECT had high sensitivity and specificity in the diagnosis of posttraumatic anosmia, with SPECT having better performances than MRI
Rombaux et al[1189]	2012	4	Prospective case series	60 patients with OD (28 postinfectious, 32 posttraumatic)	SS-TDI (baseline and follow-up) MRI: OBV Recovery	OBV correlated with OF at baseline and with the improvement of OF at follow-up
Rombaux et al[1190]	2009	4	Retrospective case series	122 patients with PIOD	SS-TDI and powder retronasal odor identification) Chemosensory ERPs OBV	OBV correlated to psychophysical (orthonasal and retronasal) olfactory tests
Rombaux et al[1191]	2006	4	Retrospective case series	25 patients with PTOD	SS-TDI and powder retronasal odor identification OBV and brain damages	OF correlated with OBV Retronasal function was more affected with more extensive cerebral lesions Parosmia was associated with smaller OBs and the presence of cerebral damage
Rombaux et al[1192]	2006	4	Retrospective case series	26 patients with PIOD	SS-TDI OBV	OBV was negatively correlated to OF, was decreased with duration of olfactory loss, and was smaller in patients with parosmia
Aiba et al[1193]	2004	4	Prospective case series	9 patients with congenital anosmia	Olfactory pathway morphology	7 patients had abnormalities of the OB, olfactory tract, OS, or gyrus rectus
Yousem et al[1194]	1999	4	Prospective case series	36 patients with PTOD 24 normosmic controls	UPSIT® OB, olfactory tract, temporal lobes	Posttraumatic lesions were mainly seen in OB, olfactory tract, subfrontal and temporal lobes OB volume correlated with identification performances; PT patients had smaller OBVs

(Continues)

TABLE VIII.3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Doty et al[1195]	1997	4	Prospective case series	268 patients with PTOD (MRI was performed in 15)	UPSIT® Morphology of olfactory-related brain structures	MRI is able to identify damage in olfactory-related brain structures
Yousem et al[1196]	1996	4	Prospective case series	25 patients with PTOD	UPSIT® Morphology of olfactory-related brain structures	88% posttraumatic patients had abnormal MRI findings Lesions mainly involved OB, olfactory tract, and inferior frontal lobes More severe OD was associated with greater OB and olfactory tract volume loss
Yousem et al[1197]	1996	4	Prospective case series	25 patients with congenital anosmia	UPSIT® Morphology of olfactory-related brain structures	Patients with congenital anosmia had aplastic or hypoplastic OB and OT

BAST-24 = Barcelona Smell Test-24; CCCRC = Connecticut Chemosensory Clinical Research Center; CT = computed tomography; ERP = event-related potential; ID = identification; IOD = idiopathic olfactory dysfunction; LOE = level of evidence; MRI = magnetic resonance imaging; OB = olfactory bulb; OB = olfactory bulb volume; OC = olfactory cleft; OD = olfactory dysfunction; OS = olfactory sulcus; PIOD = postinfectious olfactory dysfunction; POC = primary olfactory cortex; PTOD = posttraumatic olfactory dysfunction; QOD = Questionnaire of Olfactory Disorders; SNOT-22 = 22-item Sino-Nasal Outcome Test; SPECT = single-photon emission computerized tomography; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; TDI = threshold, discrimination, and identification; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

*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 (similar to a case series study).

olfactory sulcus.[1158,1159,1165,1174,1180,1184] In postinfectious olfactory loss, OBV is decreased, and the OB may exhibit signal changes with central hyper-T2 signal.[1151] Patients with PTOD exhibit typical lesions, mainly at the level of the OB, olfactory tract, temporal, and/or frontal lobes.[1157,1161,1170,1181–1183] MRI has been found to have a high accuracy in detecting PTOD.[1175] The earliest study about MRI in PTOD reported that 88% of patients had abnormal MRI findings.[1183] Therefore, MRI is of paramount importance for the medicolegal assessment of PTOD.

MRI is also interesting to evaluate the global brain morphology and olfactory pathways. Besides showing typical lesions in patients with posttraumatic olfactory loss, it has been described that OF was associated with overall MRI brain changes[1167] (one case series) but also that parosmia and phantosmia could be related to lesions in specific brain areas[1170] (one retrospective study). In addition, brain MRI is also considered to reveal potential intracranial causes underlying IOD, and, notably, to exclude brain tumors. A retrospective study[1173] evaluated the cost-effectiveness of MRI in patients with IOD 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 IOD is debatable.

It is widely acknowledged that olfactory loss may constitute an early sign of neurodegenerative diseases, such as PD or AD. Therefore, patients with idiopathic smell loss are at times considered at risk for developing ND. However, no study has investigated the usefulness of structural MRI for the early diagnosis of these diseases in patients with idiopathic smell loss.

MRI for evaluation and diagnosis of OD

Aggregate grade of evidence: C (Level 3: 12 studies; Level 4: 20 studies).

Benefit: Identification/confirmation of the etiology, exclusion of intracranial tumor, objective correlate of OF and prognosis, medicolegal 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 the gold-standard imaging procedure for the evaluation of patients with OD from nonsinonasal inflammatory causes and may be considered as an option. The use of MRI is potentially valuable in patients with congenital and posttraumatic anosmia. It can be considered in patients with IOD to exclude intracranial pathology. Its use in PIOD 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 MRI or fMRI techniques have also been used to investigate olfactory-brain–related morphology and function (Table VIII.4: 18 prospective cohort studies, one case series). These techniques are usually not feasible or useful in clinical routine practice and require a specific research environment and the use of specific devices and software.

We found seven fMRI studies (six prospective cohort studies, one case series) related to OF. These studies found that brain activation is related to OF, with decreased activation of primary and secondary olfactory cortices following olfactory stimulation in patients with posttraumatic anosmia.[1185,1186] Moreover, brain activation was found to be negatively correlated to the duration of the disease,[1186] and recruitment of neural network was associated with OF.[1187] In contrast, a study specifically assessing hyposmic patients showed similar central olfactory processing compared with controls. However, hyposmic patients had higher activation in regions associated with odor memory and motivation, possibly as a result of compensation.[1188] In patients with long-term OD, fMRI demonstrated changes in functional connectivity after 12 weeks of olfactory training (OF), albeit in a series including only a very small number of patients.[1189] 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, because of large interindividual variability. Moreover, there was no correlation between OF and fMRI parameters.[1190]

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[1191] or changes in olfactory and global brain network connectivity in patients with PTOD.[1192]

We found 10 prospective cohort studies based on advanced morphological MRI. Among these studies, nine 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 POC[1193]; another found that congenital anosmics have larger gray matter volume in both primary and secondary olfactory cortices.[1194] In patients with postinfectious olfactory loss, it has been reported that there is a gray matter volume loss in diverse brain-related olfactory areas (notably in the OFC)[1195,1196] and that OF is associated with a regain in the volume of affected regions.[1195] Patients with IOD were also found to exhibit gray matter volume loss in primary and secondary olfactory areas.[1196] Based on OF, patients with anosmia and hyposmia exhibited decreased gray and white matter volume[1197–1199] and it has been found that patients with parosmia have gray matter volume loss in regions associated with olfactory discrimination and memory.[1200] Moreover, it has been described that disease duration influenced brain atrophy since atrophy increased with duration[1161,1197] in patients with PIOD and IOD. Finally, using a deep learning model, a prospective cohort study suggested that MRI could be useful for the differential diagnosis between Parkinson-related OD and non-Parkinson OD.[1201]

Diffusion MRI has been investigated in two prospective cohort studies.[1202,1203] One study investigated patients with congenital anosmia and found that these patients have network dysfunction but intact structural integrity.[1202] Another study investigated patients with idiopathic olfactory loss, considered as at risk for developing PD, in comparison to patients with PD and normosmic controls.[1203] This study found that, on a group level, fractional anisotropy measured at the level of the substantia nigra was decreased in idiopathic patients and patients with PD in comparison to controls. This finding suggests a reduced integrity of the substantia nigra in patients with idiopathic smell loss, 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.

Use of advanced MRI techniques for evaluation or management of OD

Aggregate grade of evidence: C (Level 3: 18 studies; Level 4: two studies).

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

Harm: Minimal.

Cost: High.

Benefit-garm assessment: Balance of benefit and harm.

TABLE VIII.4 Advanced MRI techniques (requiring research environment)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Yunpeng et al[1203]	2020	3	Prospective cohort	22 patients with OD (14 congenital, 8 idiopathic) 16 normosmic controls	SS-TDI fMRI: brain activation following odorous stimulation	BOLD signal was not able to discriminate between patients with OD and controls because of large interindividual variabilities No correlation between OF and fMRI parameters
Tremblay et al[1214]	2020	3	Prospective cohort	15 patients with PD 15 patients with PIOD or sinonasal OD 15 controls	SS-TDI MRI: OBV 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[1206]	2020	3	Prospective cohort	33 patients with CA 34 normosmic controls	SS-TDI Voxel-based morphometry Cortical thickness OS depth	Morphological alterations were found in CA at the level of OFC No morphological difference at the level of the POC
Peter et al[1204]	2020	3	Prospective cohort	33 patients with CA 33 normosmic controls	SS-TDI Resting-state fMRI: functional connectivity	No difference in functional connectivity in the olfactory cortex
Chen et al[1215]	2020	3	Prospective cohort	20 patients with CA 16 normosmic controls	SS-TDI and retronasal powder test) Diffusion tensor imaging: diffusion-tensor-based network analysis; fractional anisotropy measure	Patients with CA had network dysfunction, but structural integrity (fractional anisotropy) remained intact; retronasal deficits were more associated with white matter alterations
Park et al[1205]	2019	3	Prospective cohort	16 patients with PT anosmia 12 normosmic controls	Korean SS-TDI Functional brain network connectivity (resting-state fMRI)	PT anosmia was associated with changes in olfactory and global brain network connectivity
Moon et al[1198]	2018	3	Prospective cohort	16 patients with PT anosmia 19 normosmic controls	Korean SS-TDI fMRI: brain activation responses to olfactory stimulation	Brain activation was decreased in primary and secondary olfactory cortices in patients with PT anosmia compared with controls
Yao et al[1169]	2018	3	Prospective cohort	19 patients with PIOD 19 normosmic controls	T&T olfactometer Voxel-based morphometry OBV Time since injury	PIOD was associated with gray matter volume loss in the right OFC Duration of olfactory loss was negatively correlated with OFC volume
Han et al[1199]	2018	3	Prospective cohort	40 patients with PTOD (19 hyposmia, 21 hyposmia) 19 normosmic controls	SS-TDI fMRI: brain activation to olfactory stimulation Time since injury	Patients with PTOD had decreased odor-induced brain activation Brain activation was negatively correlated to time since injury

(Continues)

TABLE VIII.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Gellrich et al[1208]	2018	3	Cohort	30 patients with PIOD 31 normosmic controls	SS-TDI assessed before and after OFC in patients) Voxel-based morphometry	Before OFC, PIOD had decreased gray matter volumes in the limbic system and thalamus; after training these volumes were significantly increased
Haehner et al[1216]	2018	3	Prospective cohort	19 patients with idiopathic smell loss 17 normosmic controls 12 patients with PD	SS-TDI, diffusion tensor imaging, diffusion characteristics, fractional anisotropy measures	Patients with PD and idiopathic smell loss had significantly reduced fractional anisotropy values in the substantia nigra compared with HCs
Pellegrino et al[1201]	2016	3	Prospective cohort	11 hyposmic patients 12 normosmic controls	SS-TDI fMRI: brain activation to olfactory stimulation	Hyposmics had similar central olfactory processing, but they had higher activation in regions associated with odor memory and motivation
Yao et al[1209]	2014	3	Prospective cohort	16 patients with IOD 16 normosmic controls	T&T olfactometer Voxel-based morphometry	Patients with IOD had reduced gray matter volume in primary and secondary olfactory areas
Peng et al[1210]	2013	3	Prospective cohort	19 anosmics 20 normosmic controls	OF (T&T olfactometer) Voxel-based morphometry	Patients with anosmia had a significant decrease in gray matter and corresponding white matter volumes Atrophy increased with disease duration
Frasnelli et al[1207]	2013	3	Prospective cohort	17 patients with CA 17 normosmic controls	Voxel-based morphometry	Patients with CA had larger gray matter volumes in the left entorhinal and piriform cortices and thicker OFC bilaterally, and left piriform cortex
Bitter et al[1213]	2011	3	Prospective cohort	22 patients with parosmia 22 hyposmic controls without parosmia (matched for OF)	Voxel-based morphometry	Parosmia was associated with gray matter volume loss in regions associated with olfactory discrimination and memory
Bitter et al[1211]	2010	3	Prospective cohort	24 hyposmic patients 43 normosmic controls	Voxel-based morphometry	Hyposmic patients had gray and white matter volume loss in several olfactory-related brain regions

(Continues)

TABLE VIII.4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Bitter et al[1212]	2010	3	Prospective cohort	14 anosmic patients 17 normosmic controls	Voxel-based morphometry	Anosmic patients had significant decrease of gray matter volume in several olfactory-related brain regions Longer disease duration was associated with increased atrophy
Reichert et al[1200]	2018	4	Case series	48 patients with OD (29 anosmia, 19 hyposmia)	SS-TDI fMRI: brain activation to olfactory stimulation	Recruitment of neural networks was correlated to OF
Kollndorfer et al[1202]	2015	4	Case series	10 patients with OD 14 HCs 7 with OD followed up after OT	SS-TDI 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

CA = congenital anosmia; fMRI = functional magnetic resonance imaging; HC = healthy control; IOD = idiopathic olfactory dysfunction; LOE = level of evidence; MRI = magnetic resonance imaging; OBV = olfactory bulb volume; OD = olfactory dysfunction; OF = olfactory function; OFC = orbitofrontal cortex; OS = olfactory sulcus; OT = olfactory training; PD = Parkinson disease; PIOD = postinfectious olfactory dysfunction; POC = primary olfactory cortex; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi.

Value judgments: These techniques require particular setup, specific analytic techniques, and expertise. Moreover, fMRI studies show a high interindividual 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 interindividual 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: four prospective cohort studies, two retrospective case series).

One prospective cohort study evaluated brain metabolism using fluorodeoxyglucose-positron emission tomography under olfactory stimulation.[1203] It showed that brain metabolism in certain brain regions is significantly different between patients with IOD and controls,[1204] with a correlation between disease duration and fluorodeoxyglucose uptake.

Two studies (one prospective cohort study and one retrospective case series) have investigated, using single-photon emission computerized tomography, 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 OBV.[1205] Also, high thallium migration was associated with a better prognosis of olfactory recovery.[1169] Three other single-photon emission computerized tomography–based studies (two prospective cohort studies and one retrospective case series) found that, after olfactory stimulation, the mean brain, frontal, temporal, and parietal perfusions were significantly lower in patients with PTOD.[1161,1206] Moreover, regional brain perfusion was able to diagnose PTOD with a high accuracy,[1175] which was even better than MRI.

Use of nuclear medicine imaging to evaluate OD.

Aggregate grade of evidence: C (Level 3: four studies; Level 4: two studies).

Benefit: Single-photon emission computerized tomography could be beneficial for the diagnosis of PTOD (eg, medicolegal 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.

TABLE VIII.5 Nuclear medicine techniques

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Micarelli et al[1217]	2017	3	Prospective cohort	11 patients with IOD 11 normosmic controls	SS-TDI Fluorodeoxyglucose-PET CT under olfactory stimulation	Brain metabolism was different in patients vs controls Negative correlation between disease duration and fluorodeoxyglucoseuptake in left temporoparietal joint
Shiga et al[1218]	2013	3	Prospective cohort	21 patients with OD 10 normosmic controls	T&T olfactometer Nasal thallium migration to the OB (SPECT-MRI) MRI: OBV	Thallium migration to the OB was lower in patients; was correlated with odor thresholds and with OBV
Gerami et al[1219]	2011	3	Prospective cohort	20 patients with PTOD 15 normosmic controls	UPSIT® SPECT after olfactory stimulation	Mean brain perfusion was significantly lower in patients with PTOD
Atighechi et al[1174]	2009	3	Prospective cohort	21 patients with PTOD 19 posttraumatic patients without OD 63 normosmic HCs	OF CCCRC-Identification MRI: OB morphology, brain lesions SPECT: brain perfusion	Posttraumatic anosmics had hypoperfusion in the frontal left parietal and left temporal lobes
Shiga et al[1182]	2017	4	Retrospective case series	24 patients with IOD	T&T olfactometer at baseline and after treatment with Japanese herbal medicine Olfacto-scintigraphy (nasal thallium administration and SPECT-CT) at baseline OBV at baseline Prognosis of recovery	High thallium migration to the OB is associated to better prognosis
Atighechi et al[1188]	2013	4	Retrospective case series	63 patients with PTOD	CCCRC olfactory test MRI: abnormalities of the OB, olfactory tract, and frontal and temporal lobes SPECT: perfusion in the frontal and temporal lobes	MRI and SPECT have high sensitivity and specificity in the diagnosis of posttraumatic anosmia, with SPECT having better performances than MRI

CCCRC = Connecticut Chemosensory Clinical Research Center; CT = computed tomography; HC = healthy control; IOD = idiopathic olfactory dysfunction; LOE = level of evidence; MRI = magnetic resonance imaging; OB = olfactory bulb; OBV = olfactory bulb volume; OD = olfactory dysfunction; OF = olfactory function; OS = olfactory sulcus; PET = positron emission tomography; PTOD = posttraumatic olfactory dysfunction; SPECT = single-photon emission computerized tomography; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; UPSIT® = University of Pennsylvania Smell Identification Test.

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 feasible (contraindications to MRI).

C | Use of validated quantitative smell tests

It is well established that patients have difficulty in assessing the degree of their own OF. 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 completely unaware of significant dysfunction until being tested.[1206–1216] Among variables that accentuate such discrepancies are older age and poorer cognition.[1217] 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 on 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, ie, tests that require a conscious response on the part of the patient and which relate private sensory experiences to antecedent physical stimulus properties. Papers that 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 OF.[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" (ie, <5-minute administration time; Table VIII.6), "moderately brief tests" (ie, 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 patients 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 cutoff values for defining abnormality are commonly noted. Some longer tests can differentiate degrees of dysfunction, eg, 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 (eg, for brief screening, more definitive clinical conclusions, research).

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 patient responses. Both tests of baseline sensitivity (eg, odor detection and recognition threshold tests, signal detection tests) and tests of suprathreshold function (eg, 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 commercially available. 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 patients, a consideration in the age of COVID-19.

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[1263]	ID	6	NR	No	Six odorants selected from wine-tasting kit Not sensitive to smoking or sex Did differentiate between complainers and noncomplainers of smell dysfunction 0.79 correlation reported with UPSIT® scores, but spurious as a result of score distributions
Alcohol Sniff Test Davidson et al, 1997[1264,1265]	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[1266]	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[1267]	ID	12	0.78	Yes	Selected 12 odors from 16 on the basis of being correctly identified by 70% of >1000 patients Statistically differentiated between normosmics, hyposmics, and anosmics but significant overlap between hyposmics and the other two groups Score of ≤6 highly suggestive of some OD May take >4 minutes
3-Item Pocket Smell Test (PST) Duff et al, 2002[1268]	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 differentiate between AD and major affective disorder (depression)
Suprathreshold Intensity Ratings Koskinen et al, 2004[1269]	IR	2 3 concentrations 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[1994]

(Continues)

TABLE VIII.6 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Commercial availability	Comments
Quick Smell Test (Q-SIT) Jackman and Doty, 2005[1270]	ID	3	0.87	Yes	A 3-item screening test with a no smell alternative In 224 consecutive patients, this test identified abnormalities in 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 cutoff score of 2, the sensitivity and specificity of detecting anosmics was 99% and 40%, respectively
Short Olfactory Screening Test Mueller and Renner, 2006[1271]	ID	5	0.77	Yes	Five odorants from the SS test chosen and compared with 20 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." Nonforced 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[1273]	ID	5	NR	No	Employs commercially available children's colored and 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 ID task Distinguishes anosmics from normosmics with high sensitivity and specificity Requires blindfolding
Parkinson Disease-Selective Odor Identification Test Bohnen et al[1275]	ID	3	NR	Yes	Three UPSIT® items identified with an accuracy of >75% in differentiating patients with PD from controls Using a cutoff of ≤1, diagnostic accuracy was 83.3% with a sensitivity of 70.3% and a specificity of 96.3%
Short Connecticut Smell Test (CST) Toledano et al, 2009[1276]	DT	1	NR	No	Single ascending method of limits threshold test using only n-butanol Normal scores <3 dilution number for patients up to 50 years of age (n = 54) and <4 for those older than this age (n = 46) Validated by determining the sensitivity and specificity of differentiating persons with nasal polyposis from those without nasal polyposis

(Continues)

TABLE VIII.6 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Commercial availability	Comments
Q-Sticks Test Hummel et al, 2010[1277]	ID	3	NR	Yes	Determined the sensitivity and specificity of 3 odors to discriminate between anosmics, hyposmics, and normosmics, as defined by SS scores Sensitivity and specificity of distinguishing anosmics from hyposmics/normosmics were 98% and 59%, respectively
OLFACAT Smell Test Mullol et al, 2015[1278]	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 9348 surveys returned to investigators Defined anosmia as not detecting any of the 4, normosmia detecting all 4, and hyposmia detecting 2 or 3 of the odorants
4-Odor NHANES Pocket Smell Test (PST) Rawal et al, 2015,[1280] and Hoffman et al, 2016[1281]	ID	4	NR	Yes	Expands 3-Item PST to 4 microencapsulated UPSIT® odorants Four-alternative responses in a folded cardboard format Uses half of the 8 odorants employed in large NHANES See 8-item NHANES listing in Table 2
6-Item Pocket Smell Test (PST) Christensen et al, 2017[1282]	ID	6	NR	Yes	Selected PST odors easily identified by Europeans to assess sensitivity and specificity in differenting patients with AD 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[1283]	ID	5	NR	Yes	Established 4-item test from 23,232,278 combinations of UPSIT® items that optimized differentiating patients with PD from normal controls Subsequent approaches on a different data set were similarly successful[64]
Ethyl Alcohol Threshold Test Calvo-Hendriquez et al, 2020[1285]	DT	1	NR	No	Provided 5 aqueous dilutions of ethanol (10% to 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 2 groups Requires preparation of stimuli

*These times vary depending on the patients. Some tests require preparation.

AD = Alzheimer disease; DQ = detection question; DT = detection threshold; ETOC = European Test of Olfactory Capabilities; ID, identification; IR = intensity rating; NHANES = National Health and Nutrition Survey; NR = not reported; OD = olfactory dysfunction; OLFACAT = Olfaction in Catalonia; PST = Pocket Smell Test; RT = recognition threshold; RQ = recognition question; SS = Sniffin' Sticks; UPSIT® = University of Pennsylvania Smell Identification Test.

All tests have a level of evidence of 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[1286]	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 Nonforced choice Used mainly coffee odor as stimulus
Phenyl Threshold Test Fordyce, 1961[1287]	RT	1 at 8 concentrations	No coefficient; reliability; shown as consistencies	No	No	Ascending nonforced-choice RT using wide-mouth sniff bottles Reliability estimated from 98 patients 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[1288]	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 at half increments until a sensation was perceived Nonforced choice
Squeeze Bottle Olfactory Threshold Test Amoore and Ollman, 1983[1290]	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

(Continues)

TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
4-Odorant Method of Limits Threshold Test Eichenbaum et al, 1983[1291]	DT	4	NR	No	No	Four ascending method of limits ID 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®) (also known as Smell ID Test [SIT]) Doty et al, 1984[1292]	ID	40	0.94	Yes	Yes	Self-administered "Scratch & Sniff" 4-alternative forced-choice ID test Norms based on 5- to 100-year-old convenience sample of 3928 persons Sex and age differentiation and percentile ranking[73] Sanitary Available in 36 language versions.
Yes-No Odor Discrimination Test Corwin, 1988[1294]	DISC	20 (2 trials each)	0.69 (number correct) 0.67 (d')	No	No	A yes:no ID test based 40 trials of 10 pairs of UPSIT® items applicable to signal detection analysis Provides a measure of odor ID 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,[1295] and Markison et al, 1993[1296]	ID	8	0.85[77]	No	No	Composed of 8 nonstandardized 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[1298]	DISC	16	0.43	No	No	Microencapsulated odorants presented in isointensive triads with one being different from the other two Number correct of 16 trials is DISC measure

(Continues)

TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
Suprathreshold Amyl Acetate Odor Intensity and Odor Pleasantness Rating Test Doty et al, 1995[1251]	IR PR	1 odor 4 concentrations	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 (B-SIT) (also known as Cross-Cultural Smell ID Test) Doty et al, 1996[1299]	ID	12	0.73	Yes	Yes	Odors with international applicability Norms based on 5- to 100-year-old convenience sample of 3760 patients Sex and age differentiation and percentile ranks Self-administered Sanitary Availability of multiple test item versions
Scandinavian Odor Identification Test Nordin et al, 1998[1300]	ID	16	0.79	No	No	Composed of 13 nonstandardized 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[1301]	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 s and different concentrations of 3 of the 5 T&T olfactometer odorants Test scores correlated with the degree of nasosinus CT opacity in a small study cohort Nonforced choice Patients found test more difficult than the CCCRC DT test with which it correlates[82]

(Continues)

TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
Smell Diskettes Briner and Simmen, 1999[1303]	ID	8	NR	No	Yes	This screening test employs odorants embedded in 5-cm × 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 patients 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[1304]	DT RT Adaptation	2 Multiple concentrations	NR	No	No	Modified blast-injection procedure of Elsberg and Levy in which DT and ID 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[1305]	DISC	1 (6 concentrations)	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[1305]	DISC	4	NR	No	No	Four fruit-like odors presented in a 12-trial match to sample task (1 same, 1 different) Total score possible is 12 Source and names of odors not provided
Retronasal Powder Olfactory Identification Test Heilmann et al, 2002[1306]	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

(Continues)

TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
Odor Memory/ Discrimination Test Choudhury et al, 2003[1307]	DISC OM	12	0.68	Yes	Yes	A 12-item, single-target, 4-alternative, forced-choice test with 10-, 30-, and 60-seccond 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[1309]	ID	40	NR	Yes	Yes	Administered 20 UPSIT® items to each side in order to develop unilateral norms based on 270 patients ranging in age from 15 to 64 years 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 patients with <12 years of education Suggests unilateral norms may aid in following the development of some neurodegenerative diseases
Odor Stick Identification Test Saito, 2006[1310]	ID	13	0.77	No	Yes	Employs odorant microcapsules that are incorporated into lipstick-like creams that are applied to paraffin papers folded and rubbed together to produce scent Employs ID 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[1312]	ID	10	NR	No	No	Ten odorants chosen to be easily identified by Jordanian individuals Apparently only asked what they smell like without alternatives Details of stimulus presentation procedure lacking

(Continues)

TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
						Reports Pearson correlation with UPSIT® of 0.98, but this is misleading since half of the patients were anosmic with Kallmann syndrome and half had high UPSIT® scores (median, 37; mean, 36.8; mode, 36)
Odorized Marker Screening Test Vodicka et al, 2007[1273]	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 ID task Distinguishes anosmics from normosmics with high sensitivity and specificity Requires blindfolding
Connecticut Smell Test (CST) Toledano et al, 2009[1276]	DT	1	NR	No	No	Single ascending method of limits threshold test using n-butanol Normal scores <3 dilution number for patients up to 50 years of age (n = 54) and <4 for those older than 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[1313]	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 (Choudhury et al[87]) except microencapsulated odorants not used
Dusseldort Odor Discrimination Test Weierstall and Pause, 2012[1314]	DISC	15	0.66	No	No	Based on extensive research of odorant mixture discriminations to optimize reliability relative to test length

(Continues)

TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
						Each stimulus is a mixture of 4 odorants selected from a total of 6 chemicals In 102 patients, weak significant correlation ($P < 0.05$) with UPSIT® ($r = 0.19$), but not with SS DISC test ($r = 0.11$, not significant)
Italian Olfactory Identification Test (IOIT) Maremmani et al, 2012[1315]	ID	33	0.96	Yes	No	Employed Italian-specific microencapsulated odorants on white cardboard rectangles 35 × 55 mm High reliability reflects inclusion of PD and healthy normal data in the same analysis Sensitive to sex and age. 95% cutoff reference limits provided for third lst to 7th decades for each sex and both sexes combined
Indian Smell Identification Test (INSIT) George et al, 2013[1316]	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 SS 12-item odor ID test ($r = 0.75$) in patient group containing 53 normal and 50 PD patients Anosmia/hyposmic considered with a score <5[97]
NIH Toolbox Odor Identification Test Dalton et al, 2013[1279]	ID	9 (adults) 5 (children)	0.58 (adults) 0.45 (children)	Yes	Yes	Scratch & sniff cards useful for testing adults and children Normed on 1446 children and 2884 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- to 7-year olds has very low reliability ($r = 0.20$), but for adults is similar to that of the English version ($r = 0.52$)[98]

(Continues)

TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
Open Essence Odor Identification Test Okutani et al, 2013[1319]	ID	12	NR	Yes	Yes	Odorants presented in sealed envelopes that are released when opened Six alternatives present for each odorant In a study of 176 medical students (median age, 24 years), males exhibited a 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[1320]	ID	15	NR	No	No	Employed 15 nonstandardized grocery store stimuli presented in glass bottles to 81 volunteers Four response alternatives per odorant were presented Percentage of correct responses noted >70% for 13 of the 15 test items No sex differences observed
Olfaction Function Field Exam (OFFE) Kern et al, 2014[1321]	ID DT	5 ID 2 Threshold	ID: NR Threshold: 0.56[101]	No	No	Employs abbreviated n-butanol and androstandienone threshold tests and a nonforced-choice 5-item odor ID test Used in the NSHAP survey of 2304 patients aged 36–99 years Dysfunction defined as detecting ≤2 of the 5 odors in ID test and ≤4 of the 6 n-butanol concentrations For androstandienone, normosmics are those who detect all 4 concentrations, hyposmics 2 or 3, and anosmics one or none
Retronasal Olfactory Test Croy et al, 2014[1322]	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 patients determined orthonasally Correlates with TDI SS orthonasal test 0.80

(Continues)

TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
Self-Administered Computerized Olfactory Testing System Jaing et al, 2015[1323]	DT	1 17 concentrations	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 (PST) Rawal et al, 2015,[1280] and Hoffman et al, 2016[1281]	ID	8	0.66–0.90	Yes	Yes	Composed of UPSIT® odorants contained in 2 folded PST of 4 odors each Employed in large NHANES with multiple variables collected that can be empirically assessed Dysfunction is defined as missing ≥3 test items
Sniffin' Test of Odor Memory (TOM) Croy et al, 2015[1324]	OM	8	0.70	Yes	No	In this episodic memory task, patients were exposed to 8 odors and thereafter tested by a yes:no odor recognition task with the odors interspersed with 8 other odors ID then determined Both recognition and ID negatively impacted by age Percentiles available for 3 age groups based on 96 patients 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[1326]	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 ID (total score of 50 possible) Validated on 187 patients Correlates 0.87 with traditional Chinese language UPSIT®

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TABLE VIII.7 (Continued)

Test name and author/s	Test type	No. of odors or items	Reliability coefficient	Normative data available	Commercially available	Comments
Snap & Sniff Odor Threshold Test Doty et al. (2018)[1327,1328]	DT	1 odor 15 concentrations 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 on 414 patients
Snap & Sniff Odor Discrimination Test Doty, 2019[1329]	DISC	20	NR	Yes	Yes	Uses wands to 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 patients
Affordable Rapid Olfaction Measurement Array Test Villwock et al, 2020[1330]	ID	14 2 concentrations each	0.85	No	No	Uses essential oils as stimuli If patients detects a scent, a 4-alternative forced-choice odor ID task Differentiates between normals and nasosinus patients Correlates 0.75 with UPSIT®
Retronasal Powder Olfactory Identification Test II Yoshino et al, 2020[1331]	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 2-point difference from 5th to 95th percentiles in normal group Remarkably, test correlates higher than its own reliability values with SS tests (ID, 0.88; D, 0.84; threshold, 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[1332]	ID	30	NR	No	No	In this study of 150 patients, a 30-odor ID test applicable in Thailand was compared with the UPSIT® and found a 0.64 correlation between the 2 tests

*These times will vary depending on the patients. Some tests require preparation.

B-SIT = Brief Smell Identification Test; CCCRC = Connecticut Chemosensory Clinical Research Center; CT = computed tomography; DISC = discrimination; DT = detection threshold; ID, identification; IR = intensity rating; NHANES = National Health and Nutrition Survey; NIH = National Institutes of Health; NR = not reported; NSHAP = National Social Life, Health, and Aging Project; OM = odor memory; PD = Parkinson disease; PEA = phenylethyl alcohol; PST = Pocket Smell Test; PR = pleasantness rating; RT = recognition threshold; SS = Sniffin' Sticks; TDI = threshold, discrimination, and identification; T&T = Toyoda and Takagi; UPSIT® = University of Pennsylvania Smell Identification Test.

All tests are a level of evidence of 5.

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

Test name and author/s	Test type	No. of odors items	Reliability coefficent	Normative data available	Commercially available	Comments
9-Odor Ascending Threshold Test Proetz, 1924[1333]	DT RT	9 with multiple dilutions	NR	No	No	Employed multiple concentrations of each of 9 odorants selected on the basis of chemical makeup, low trigeminal impact, and dynamic range in ascending nonforced-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[1334]	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 a counterbalanced fashion with each threshold being obtained 6 times for each odorant by 24 patients Blanks only used as comparison if patient not sure of sensation
Henkin Olfactory Threshold Test Henkin and Bartter, 1966[1335]	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, 1 odorant + carrier solution and carrier solution alone 13 concentrations employed Threshold defined as lowest concentration in which 2 successive correct responses occurred while 2 consecutive incorrect responses occurred at next lower concentration Medians and ranges presented for 41 normal volunteers aged 6 to 59 years Pyridine values at major variance from the Amoore Threshold Test[116]
Short-Term Odor Memory Tests Engen et al, 1973[1337]	OM	25 but different for individual patients	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 seconds is unimpaired Among the first to provide a test of short-term odor memory

(Continues)

TABLE VIII.8 (Continued)

Test name and author/s	Test type	No. of odors items	Reliability coefficent	Normative data available	Commercially available	Comments
n-Octanol Absolute and Difference Threshold Tests Rovee et al, 1973[1338]	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[1339] and Takagi, 1989[1340,1341]	DT and 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 because of bad smell of some stimuli Ascending method of limits with lowest concentration detected defined as DT and lowest concentration with quality RT Nonforced-choice Norms not sex- or age-corrected, with 5 categories of dysfunction based on men and women aged 18 to 25 years
Koelega Threshold Test Koelega, 1979[1342]	DT	1 odor 9 concentrations	0.65 bilateral 0.51 right 0.59 left	No	No	Amyl acetate method of constant stimuli thresholds for 20 men and 20 women No left:right differences found College-aged students No determination of sex effects No norms
Ascending Pyridine, Thiophene and PEA Detection Threshold Tests Perry et al, 1980[1343]	DT	3 odors 19 concentrations	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 patients tested Age but not sex effects observed for thiophene and pyridine, but not phenyl ethanol

(Continues)

TABLE VIII.8 (Continued)

Test name and author/s	Test type	No. of odors items	Reliability coefficent	Normative data available	Commercially available	Comments
Signal Detection Tests of Odor Sensitivity and Discrimination Potter and Butters, 1980[1343]	SD	1 odor for sensitivity 8 odors for DISC	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 DISC, 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[1336]	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 (CCCRC) Test Cain et al, 1983[1346]	ID DT	10 ID 1 Threshold	ID: 0.60* Threshold: 0.68[127]	No	No	Composed of an ascending forced-choice method of limits n-butanol squeeze bottle threshold test plus ID test of 10 common nonstandardized household items Ammonia, Vicks vapor rub, and wintergreen are included as trigeminal stimulants Response list of 20 odorants used to cue patient responses
4-Odorant Method of Limits Threshold Test Eichenbaum et al, 1983[1291]	DT	4	NR	No	No	Four ascending method of limits ID test with blank control on each trial based on 10 two-fold water dilutions of 4 odorants: almond (McCormick),

(Continues)

TABLE VIII.8 (Continued)

Test name and author/s	Test type	No. of odors items	Reliability coefficent	Normative data available	Commercially available	Comments
						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[1348]	DT	1 odor 14 concentrations	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 Wright, 1987[1351]	ID	10	0.91[132]	No	No	Indicates that performance ≥80% reflects normality Attempts to explore confusions and thereby categorize dysosmias Limited by the choice of odorants to which confusions can be made Percent correct correlates highly with UPSIT® scores Norms based on convenience sample 100 of persons
Utrecht Odour ID Test Hendriks, 1988[1353]	ID	18 or 36	0.68—0.77	Yes	No	Composed of 2 subsets of 18 natural odorants designed for both the otolaryngology 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[1354]	OM DISC	12	0.68[31]	No	No	OM and DISC tests based on: (1) multiple target testing, and (2) single target testing with 10-, 30-, and 60-second delay intervals

(Continues)

TABLE VIII.8 (Continued)

Test name and author/s	Test type	No. of odors items	Reliability coefficent	Normative data available	Commercially available	Comments
						The latter test has been shown to be age- and sex-related[87]; however, performance among these short-memory intervals is relatively constant, in accord with earlier studies
Combined Olfactory Test Robson et al, 1996[1355]	ID and RT	9 ID 1 Detection	0.87	No	No	Combined scores from a 9-odor ID test and an n-butanol threshold test for 133 patients 12—80 years of age (mean, 37.5 years No indication of sex differences No percentiles, but can be calculated from figures
Sniffin' Sticks Test Kobal et al, 1996[1356]	ID and DT	12 and 16	ID: 0.73, DT: 0.54 Combination: 0.72[34]	Yes	Yes	146 patients tested, with norms based on 5- to 100-year-old convenience sample of 9139 patients[137] Sex and age differentiation and percentile ranks Divides function into 3 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[1359]	ID	20	0.75	No	No	A 20-odor ID test Odors presented in plastic jars Age-related normative sample based on 97 patients Raw scores converted to T scores T scores <30 indicative of smell loss Combined with n-butanol threshold test
Random Olfactory Sensitivity Procedure Kobal et al, 2001[1360]	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 nonforced-choice Correlates well with standard staircase threshold procedure ($r = 0.77$)

(Continues)

TABLE VIII.8 (Continued)

Test name and author/s	Test type	No. of odors items	Reliability coefficent	Normative data available	Commercially available	Comments
Odor Recognition Memory Test Öberg et al, 2002[1305]	OM	48	NR	No	No	Patients first presented with a set of 24 odors, which they rated on familiarity, intensity, pleasantness, irritability, edibility) After a delay interval during which 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 detection ananalysis
European Test of Olfactory Capabilities (ETOC) Thomas-Danguin et al, 2003[1361]	ID and DT	16	0.90	NR	No	Test based on a combination of an odor ID and DISC 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 IDs Validated in France, Sweden, and the Netherlands
Biolfa Olfactory Test Bonfils et al 2004[1362]	DT and RT	3 and 8	NR	No	No	Employs 9 aqueous concentrations each of 3 odorants to determine DTs using a forced-choice staircase procedure Patients were 67 normal and 155 patients with complaints of smell dysfunction Eight odorants at 4 concentrations used for odor recognition performances
Barcelona Smell Test Cardesin et al, 2006[1363]	DT and RT	24	NR	No	No	Twenty cranial nerve I and 4 contingent negative variatio odors presented in glass jars Patients asked: (1) if they smelled something, (2) if they recognized the odor, and (3) to identify each odor from 4 response alternatives

(Continues)

TABLE VIII.8 (Continued)

Test name and author/s	Test type	No. of odors items	Reliability coefficent	Normative data available	Commercially available	Comments
						In validation study, 120 patients 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[1364]	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 DISC task using semantically related odors (eg, 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[1365]	ID	23	0.75	No	No	Uses hard sweet candies of unknown manufacturers to assess retronasal OF in children and adults Scores correlate well with orthonasal smell tests In 230 children and 123 adults, score of ≤13 differentiated anosmics from normosmics with a sensitivity of 94% and a specificity of 83%
Extended Sniffin' Sticks test Haehner et al, 2009[1366]	ID DT DISC Combination	32	ID: 0.88 DT: 0.92 DISC: 0.80 Combination: 0.93	Yes	Yes	Extends SS 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

(Continues)

TABLE VIII.8 (Continued)

Test name and author/s	Test type	No. of odors items	Reliability coefficent	Normative data available	Commercially available	Comments
Lyon Clinical Olfactory Test Rouby et al, 2011[1367]	ID DT	ID: 16 Threshold: 2 5 concentrations each	NR	No	No	Combines a 4-alternative forced-choice ID 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 patients tested twice noted no meaningful differences
Monell Extended Sniffin' Sticks Identification Test (MONEX-40) Freiherr et al, 2011[1368]	ID	40	0.68	No	No	Added 24 odorants to the standard 16-item SS to provide a test comparable to the 40-item UPSIT® Administered to 259 healthy young patients, of whom 72 were retested to assess reliability Unlike original 16-item SS, sensitive to sex No normative data
Smell-S and Smell-R Olfactory Tests Hsieh et al, 2017[1369]	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 SS phenyl ethanol DT 0.87
Leicester Semi-automated Olfactory Threshold Test Philpott et al[1370a]	DT	8	0.78	Yes	No	Semiautomated delivery of 8 logarithmic dilutions of odorant Consistent odorant thresholds achieved with mean concentration of 10-4 Good test-retest reliability

DIFF T = difference threshold; DISC = discrimination; DISC ON = discrimination and odor naming test; DT = detection threshold; ID = identification; NR = not reported; OM = odor memory; OPM = odor-picture matching test; PEA = phenylethyl alcohol; RT = recognition threshold; SD = signal detection; SS = Sniffin' Sticks; UPSIT® = University of Pennsylvania Smell Identification Test.
All tests are a level of evidence of 5.

TABLE VIII.9 Olfactory tests designed for children

Test name and author/s	Testtype	No. of odors or items	Reliability coefficient	Estimated test duration	Normative data available	Commercially available	Comments
San Diego Odor Identification Test Murphy et al, 1992[1295,1296]	ID	8	0.85[77]	≈10 minutes	Limited	No	Composed of 8 nonstandardized 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[1371]	ID	5	NR	<5 minutes	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 in children older than 12 years likely denotes OD
Match-to-Sample Odor Discrimination Test (MODT) Richman et al[1372]	DISC	Multiple sets of 3-item tests (probe plus probe and distractor)	NR	<15 minutes	No	No	Tested 44 boys and 21 girls ranging in age from 2 to 18 years on a match-to-sample test A "probe" microencapsulated odor was first smelled followed by 2 odors placed in front of the child The child indicated which one smelled like the probe A total of 20 trials were performed To vary the difficulty level for different age groups, 4 age-appropriate odorant sets were developed The respective performances for participants aged 4, 5 to 9, 10 to 12, 13 to 15, and 16 to 18 years were 61%, 87%, 91%, 97%, and 98%, respectively
Odor Identification Test for Children Laing et al, 2008[1373]	ID	16	0.45[59]	≈5 minutes	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 Cutoff points at 10th percentiles indicated for 5-, 6-, and 7-year-olds, as well as adults

(Continues)

TABLE VIII.9 (Continued)

Test name and author/s	Testtype	No. of odors or items	Reliability coeffi-cent	Estimated test duration	Normative data available	Commercially available	Comments
							No differences between 3 child age groups No sex effects
Candy Smell Test Renner et al, 2009[1365]	ID	23	0.75	≈20 minutes	Limited	No	Uses hard sweet candies of unknown manufacturers to assess retronasal OF in children and adults Scores correlate well with orthonasal smell tests In 230 children and 123 adults, score of ≤13 differentiated anosmics from normosmics with a sensitivity of 94% and a specificity of 83%
NIH Toolbox Children's Test Dalton et al, 2011[1374]	ID	6		<7 minutes	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, and easy-to-administer test 1446 children were studied to provide normative data that were validated against the UPSIT® and B-SIT
Pediatric Smell Wheel (PSW) Cameron and Doty, 2013[1375]	ID	11	0.70	<5 minutes	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 in 152 children and adults No normative data but scores <5 suggestive of anosmia
Test for Screening Olfactory Function in Children Dzaman et al, 2013[1376]	ID	6	NR	<5 minutes	Limited	No	Six odorants chosen from a test of 21 odorants given to 37 children aged<5 years, 30 aged 5 to7 years, and 18 aged 7 to10 years Odors presented in bottles Score of ≥4 considered normal, being achieved by 96.5% of the 85 children
Universal Sniff (U-Sniff) Test Schriever et al, 2018[1377]	ID	12	0.83	<10 minutes	Yes	No	Odorants selected to be identified by children (mean [SD] age, 6.3 years [0.5 years]) Collaboration among 18 countries Employs SS 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

(Continues)

TABLE VIII.9 (Continued)

Test name and author/s	Testtype	No. of odors or items	Reliability coefficient	Estimated test duration	Normative data available	Commercially available	Comments
Paediatric Barcelona Olfactory Test Mariño-Sánchez et al, 2020[1378]	ID DT	ID: 6 DT: 6 Concent	ID: 0.83 Threshold: 0.73	<3 minutes	Limited	NR	A test for 6- to 17-year-old children based on 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- to 11-year-olds 4/6 and for 12- to 17-year-olds 5/6 For threshold: 2/6
Kradeo Odor Identification Test Concheiro-Guisan et al, 2012[1379]	ID	7	NR	<10 minutes	No	No	Child required to name each of 7 odors without cues or response alternatives Credit given to alternative names (eg, 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 2 groups

B-SIT = Brief Smell Identification Test; DISC = discrimination; DT = detection threshold; ID = identification; NR = not reported; NIH = National Institutes of Health; OF = olfactory function; SS = Sniffin' Sticks; T&T = Toyoda and Takagi; UPSIT® = University of Pennsylvania Smell Identification Test.
All tests are a level of evidence of 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 individuals 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, ie, require indication of a specific odorant quality from a list of alternatives, although some include a "no odor" alternative. The latter makes it impossible to establish a likelihood of malingering based on improbable response probabilities and to control for response biases (eg, 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 cannot 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.[1218]

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.[1219] A common index of this process is termed a *just noticeable difference* (or ΔS, also known as a Weber ratio), a value that is generally, but not completely, consistent among a range

of concentrations of a given odorant. Just noticeable differences are sensitive to age and have been measured in clinical settings,[1220] 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 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, eg, 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 participant's 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 straightforward 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 are performed. Such tests were developed following the classical Peterson and Peterson short-term memory test for verbal material.[1221] Other memory tests require a participant 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, eg, "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.[1222] 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 buildup 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.[1223] The most common rating scales used clinically are category scales and visual analog scale (VAS) or line scales. In category scaling, the perceived intensity is indicated according to specific categories (eg, weak, moderate, and strong); in VAS, 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 patients 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.[1224] It should be noted that, unlike tests that require forced-choice responses (eg, 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 with 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.[1225] Although, in general, persons with high thresholds (ie, 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 (ie, so-called specific anosmias). Unfortunately, the concepts of detection and recognition are commonly confounded in threshold test procedures (eg, having a patient 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.[1226] 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, ie, epithelial, OF. However, this is clearly not the case. Even detection threshold tests require cognitive processes such as working and short-term memory (eg, discerning a stimulus from blanks in a temporal sequence[1227]) and are impacted by top-down centrally mediated decision processes.[1227] Indeed, threshold tests, like tests of odor identification and discrimination/memory, have been shown to correlate with neuropsychological measures of verbal and visuospatial memory.[1228] Importantly, threshold measures are sensitive to lesions in higher order brain structures such as those observed in AD,[1212] multiple sclerosis,[1229] and epilepsy.[1230] Moreover, given the greater variability and lower reliability of most threshold tests compared with 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 on 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, eg, 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, ie, the sharpness of the buildup in performance among a given concentration gradient, only rarely is the method of constant stimuli used clinically. This is because of 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.[1231] Versions of this procedure have employed methods to blast boluses of odorants into the nose to minimize impact of sniffing or breathing, the 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 the individual's responses within the perithreshold region. An average of the reversals, ie, points of upward or downward transitions, provides the threshold estimate. Although double staircase procedures,[1232] ie, 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,[1233,1234] they are rarely employed in olfaction because of 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.[1235]

Signal Detection Tests

Signal detection tests require individuals to differentiate between low levels of an odorant, usually a single concentration established for each patient separately, and blank stimuli, although subtle quality differences between stimuli can also 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 individual, including the liberalness or conservativeness of the individual at any one time

in reporting the presence or absence of the signal, ie, the individual's response criterion. The advantage over threshold testing is that signal detection analysis can independently differentiate an individual's response criterion from his or her sensitivity, per se. Thus, a more emotional individual 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 individual. 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, ie, measurement consistency over time.[1236] Reliability is a prerequisite for validity. However, reliability coefficients, which are the main measure of such consistency among individuals of a group, depend on the variation in test scores and can be misleading when distributions of scores are restricted, eg, 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.[1236] 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 among 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 (Tables VIII.10-VIII.12), 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.

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,[1237,1238] and vary in terms of their reliabilities.[1236,1239] In one study employing SS 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.[1238]

It is important to recognize that operational terms used to describe olfactory tests (eg, detection, identification, discrimination, memory) are not pure representatives of independent physiologic or psychologic chemosensory processes signified by their names.[1223] The correlations among such tests are a testament to this fact (Table VIII.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 to the OC in some individuals. A common way to test each side of the nose separately is to occlude the nontested side with a piece of tape. Microfoam tape (3M Corporation) 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 on the purpose that is intended. In general, forced-choice tests of odor identification are preferred to other types of tests based on

TABLE VIII.10 Correlations among extant psychophysical olfactory tests

Study author	Age, mean (SD or range), year	No. of patients (male/female)	Study groups	Correlated tests	Correlation coefficients	*P* value
Doty et al, 1984[1292]	42.4 (18.9)	64	Healthy patients	UPSIT® vs threshold (PEA)	0.89	0.001
			Healthy minus anosmic patients	UPSIT® vs threshold (PEA)	0.79	0.001
Stevens and Cain, 1987[1380]	77 (70–90)	NR	Healthy patients	ID vs threshold (isoamyl butyrate)	0.51	0.02
				ID vs threshold (benzaldehyde)	0.56	0.006
				ID vs threshold (d-limonene)	0.63	0.003
	21.0 (18–24)	NR	Healthy patients	ID vs threshold (isoamyl butyrate)	0.30	NS
				ID vs threshold (benzaldehyde)	0.21	NS
				ID vs threshold (d-limonene)	0.16	NS
Cain et al, 1988[1381]	47.2 (6–85)	670 (NR)	Mixed and S&T clinic patients	ID versusvsvs Threshold threshold (n-butanol)	0.77	0.001
Cain and Rabin, 1989[1382]	1: 46.5 (9–75) 2: 44.6 (18–33)	24/26 22/36	S&T clinic patients	UPSIT® vs butanol threshold (2 sessions with different patients; 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[1347]	37.3 (NR)	10/22	Healthy patients	Pyridine threshold vs butanol threshold	0.74	0.001
				Pyridine threshold v isoamyl butyrate threshold	0.86	0.001
				Pyridine threshold vs 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

(Continues)

TABLE VIII.10 (Continued)

Study author	Age, mean (SD or range), year	No. of patients (male/female)	Study groups	Correlated tests	Correlation coefficients	*P* value
Doty et al, 1994[1238]	45.8 (20.2)	37/60	Healthy patients	UPSIT® vs butanol threshold	0.41	0.001
				UPSIT® vs T&T detection threshold (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	0.49	0.001
				UPSIT® vs PEA threshold (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[1383]	49.5 (18.5)	55/52	Healthy patients	SS-ID vs SS-T (butanol)	0.54	0.001
				SS-ID vs SS-D	0.56	0.001
				SS-T (butanol) vs SS-D	0.66	0.001
				SS-ID vs CCCRC ID test	0.50	0.001
				SS-ID vs CCCRC threshold (butanol)	0.24	0.001
				SS-T vs CCCRC ID test	0.38	0.001
				SS-T vs CCCRC threshold (butanol)	0.34	0.001
				SS-D vs CCCRC ID	0.35	0.001
				SS-D vs CCCRC threshold	0.31	0.001
				CCCRC ID vs CCCRC threshold	0.29	0.001
Kondo et al, 1998[1393]	38.2	40/40	S&T clinic patients	T&T detection vs UPSIT®	0.53	0.001
				T&T recognition vs UPSIT®	0.70	0.001
Nordin et al, 1998[1300]	(15–79)	21/21	Healthy patients	UPSIT® vs SOIT	0.76	0.001
				CCCRC threshold vs SOIT	0.60	0.001
Lehrner et al, 1999[1384]	38.4 (18–90)	31/65	Healthy patients	Odor ID vs n-butanol threshold	0.31	0.01
				Odor ID vs odor memory	0.69	0.01

(Continues)

TABLE VIII.10 (Continued)

Study author	Age, mean (SD or range), year	No. of patients (male/female)	Study groups	Correlated tests	Correlation coefficients	*P* value
				Odor memory vs n-butanol threshold	0.31	0.01
Seeliger et al, 1999[1385]	19–61	22/17	Patients with Usher syndrome	SS-ID vs SS-D	0.09	NS
				SS-ID vs SS-T (butanol)	0.01	NS
				SS-D vs SS-T (butanol)	0.14	NS
Kobal et al, 2001[1360]	47.0 (19–78)	45/52	S&T cinic patients	Random test vs SS-D	0.71	0.001
				Random test vs SS-T (butanol)	0.77	0.001
				Random test vs SS-ID	0.74	0.001
				SS-ID vs SS-D	0.79	0.001
				SS-ID vs SS-T (butanol)	0.75	0.001
				SS-D vs SS-T (butanol)	0.69	0.001
Koskinen et al, 2004[1269]	49.5 (15–84)	15/33	S&T clinic patients	SS-T (butanol) vs SS-D	0.25	NS
				SS-T (butanol) vs SS-ID	0.44	0.01
				SS-T (butanol) vs B-SIT	0.42	0.01
				SS-T (butanol) vs ETOC detection	0.34	0.05
				SS-T (butanol) vs ETOC ID	0.31	0.05
				SS-T (butanol) vs odor intensity	0.19	NS
				SS-D vs SS-ID	0.53	0.01
				SS-D vs B-SIT	0.54	0.01
				SS-D vs ETOC odor detection	0.37	0.05
				SS-D vs ETOC odor ID	0.59	0.01
				SS-D vs odor intensity	0.43	0.01
				SS-ID vs B-SIT	0.83	0.01
				SS-ID vs ETOC odor detection	0.79	0.01
				SS-ID vs ETOC ID	0.85	0.01
				SS-ID vs odor intensity	0.64	0.01
				B-SIT vs ETOC odor detection	0.73	0.01
				B-SIT vs ETOC ID	0.82	0.01
				B-SIT vs odor intensity	0.56	0.01
				ETOC odor detection vs ETOC odor ID	0.84	0.01
				ETOC odor detection vs odor intensity	0.66	0.01
				ETOC ID vs odor intensity	0.57	0.01

(Continues)

TABLE VIII.10 (Continued)

Study author	Age, mean (SD or range), year	No. of patients (male/female)	Study groups	Correlated tests	Correlation coefficients	*P* value
Tsukatani et al, 2005[1302]	38.1 (15.6)	30/45	S&T clinic patients	Jet Stream Olfactometer recognition threshold vs CCCRC ID	0.78	0.01
				Jet Stream Olfactometer detect threshold vs CCCRC threshold	0.68	0.01
Kobayashi et al, 2007	55 (16)	23/27	S&T clinic patients	OSID (13, 11, and 8 items) vs CCCRC ID test	0.80, 0.82, and 0.83	0.001
				OSID (13, 11, 8 items) vs CCCRC threshold test	0.74, 0.76, and 0.76	0.001
				OSID (13, 11, and 8 items) vs CCCRC composite	0.80, 0.82, and 0.83	0.001
Luzzi et al, 2007[1364]	71 (8)	7:7	Patients with AD	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 est	0.78	0.005
Tourbier and Doty, 2007[1386]	59.7 (15.6)	51:81	S&T clinic patients	UPSIT® vs ODT (PEA)	0.84	0.001
				UPSIT® vs ODMT	0.67	0.001
				ODT (PEA) vs ODMT	0.64	0.001
Lötsch et al, 2008[1387]	35.2 (16.2)	916/1160	S&T clinic patients	SS-ID vs SS-D	0.26	0.001
				SS-ID vs SS-T (butanol)	0.28	0.001
				SS-D vs SS-T (butanol)	0.26	0.001
Hedner et al, 2010[1252]	57.2 (13.8)	64/106	Healthy patients	SS-ID and SS-D	0.22	0.01
				SS-ID vs SS-T (butanol)	0.17	NS
				SS-D vsSS-T (butanol)	0.24	0.01
Hong et al,[1388]	40.87	128/83	Healthy and S&T clinic 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

(Continues)

TABLE VIII.10 (Continued)

Study author	Age, mean (SD or range), year	No. of patients (male/female)	Study groups	Correlated tests	Correlation coefficients	*P* value
Mahmut et al, 2012[1389]	20 (NR)	39/40	Healthy patients	SS-ID vs SS-D	0.28	0.001
				SS-ID vs SS-T (butanol)	0.34	0.001
				SS-D vs SS-T (butanol)	0.28	0.001
Weierstall and Pause, 2012[1314]	23.5 (3.7)	52/52	Healthy patients	DODT vs UPSIT®	0.19	0.05
				DODT vs PEA threshold	0.14	0.10
				UPSIT® vs SS-D	0.25	0.01
Soler et al, 2016[1390]	52.7 (16.1)	49/61	Rhinosinusitis	SS-ID vs SS-D	0.70	0.001
				SS-ID vs SS-T (butanol)	0.69	0.001
				SS-D vs SS-T (butanol)	0.62	0.001
Doty et al, 2019[1327]	58.0 (16.10)	327/409	S&T clinic patients	UPSIT® vs SS-T (PEA)	0.65	0.001
				UPSIT® vs SS-T (PEA)	0.63	0.001
				SS (PEA) vs STT (PEA)	0.67	0.001
Kasemsuk et al, 2020[1332]	42.7 (15–84)	38/112	112/38	UPSIT® vs TOIT	0.64	0.001
Aniteli et al, 2020[1391]	20–80	100	Healthy and S&T clinic patients	CCCRC ID vs B-SIT right nostril	0.90	0.001
				CCCRC ID vs B-SIT left nostril	0.90	0.001
Tian et al, 2021[1392]	50.1 (27–77)	14/24	Patients with PVOD	SS-ID vs SS-D	0.80	0.001
				SS-ID vs SS-T	0.55	0.001
				SS-D vs SS-T	0.48	0.001

AD = Alzheimer disease; CCCRC = Connecticut Chemosensory Clinical Research Center; DODT = Dusseldorf Odour Discrimination Test; ETOC = European Test of Olfactory Capabilities; ID = identification; NR = not reported; NS = not significant; ODT = odor detection threshold; ODMT = Odor Discrimination/Memory Test; PEA = phenylethyl alcohol; PEMEC = d,l-beta-phenylethylmethylethylcarbinol; PVOD = postviral olfactory dysfunction; S&T = smell and taste; SD = standard deviation; SOIT = Scandinavian Odor-Identification Test; SS = Sniffin' Sticks; SS-D = Sniffin'Sticks discrimination only; SS-ID = Sniffin' Sticks identification only; SS-T = Sniffin' Sticks threshold only; STT = Smell Threshold Test; T&T = Toyoda and Takagi; TOIT = Thai Odor-Identification Test; UPSIT® = University of Pennsylvania Smell Identification Test.

reliability, their correlation with other types of tests, and practicality. A number of tests 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 (eg, four 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 convert them to *z* scores or other appropriate metrics and implement well-established statistical methods that

TABLE VIII.11 Section evidence summary: Use of validated survey QOL testing

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Soler et al[1404]	2016	3	Prospective cohort	121 patients with CRS who underwent ESS	QOD-NS UPSIT®	Olfactory QOL worse with polyps and asthma Baseline QOD-NS and UPSIT® scores had moderate correlation
Mattos et al[1405]	2017	3	Prospective cohort	109 patients with CRS	QOD-NS SS-TDI Correlations between olfactory metrics and patient/disease factors	QOD-NS correlates with TDI, SNOT-22 QOD-NS can screen for OD based on receiver operating characteristic analysis
Thomas et al[1406]	2020	3	Prospective cohort	48 patients with CRS treated medically, short-term follow-up	Endoscopy scores SS-TDI QOD-NS SNOT-22	Medical treatment of CRS was associated with short-term improvements in olfactory QOL, without improvement in OF OF did not associate with QOL measures
Hinz et al[1407]	2019	3	Cross-sectional, community-based	7267 individuals not screened for CRS	SS-ID (12 odors) SF-8 GAD-7 scale LOT-R SWLS	Negligible associations were identified between OD and QOL among multiple nonolfactory QOL metrics in a community (non-CRS) population
Katotomichelakis et al[1410]	2014	3	Prospective cohort with control arm	111 patients with CRS who underwent ESS 48 healthy patients	SS-TDI QOD BDI SF-36	OD and polyp status were associated with improvement in all QOL measures after ESS
Schlosser et al[1411]	2017	3	Prospective cohort	221 patients with CRS	UPSIT® QOD-NS Associations between olfactory measures and health care use, productivity, and medication use	Impaired olfactory QOL is associated with worse economic and productivity measures and greater medication use
Prajapati et al[1412]	2020	3	Prospective cohort study	81 patients with COVID-19, 54 of whom reported smell loss	Olfaction scores via VAS B-SIT	Self-reported smell loss had good discriminative ability to identify abnormal B-SIT scores Moderate associations were found between VAS and B-SIT scores ($r = 0.59$)
Qui et al[1413]	2020	4	Multicenter case series	394 patients with COVID-19, 60 completed QOD	QOD 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

(Continues)

TABLE VIII.11 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Seo et al[1414]	2020	4	Single-center case series	62 patients with mild COVID-19 symptoms, admitted for surveillance	QOD-NS B-SIT Gustatory symptoms: Likert scale Gustatory function: 6-n-propylthiouracail, phenylthiocarbamide, and control strips	QOD and B-SIT scores were abnormal, as were measures of gustatory function in this cohort
Desiato et al[1408]	2020	3	Prospective cohort	221 adult patients without otolaryngologic symptoms	SS-TDI QOD-NS Olfactory VAS De Jong Gierveld Loneliness Scale University of California Los Angeles Loneliness Scale	Both OD and measures of loneliness were common and correlated in a community-based sample of patients
Zou et al[1409]	2021	3	Prospective, multicenter cohort from 8 S&T centers in Germany, Austria, and Switzerland	763 adult patients	QOD SS-TDI VAS for self-assessment	Olfactory-related QOL was associated with SS, age, and self-assessed OD Patients with PIOD and PTOD had worse QOL than those with sinonasal OD and IOD
Erskine et al[1416]	2019	4	Qualitative analysis of unstructured written patient accounts from an S&T clinic	71 patients who contacted an S&T clinic	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; B-SIT = Brief Smell Identification Test; CRS = chronic rhinosinusitis; ESS = endoscopic sinus surgery; GAD-7 = General Anxiety Disorder 7-Item; IOD = idiopathic olfactory dysfunction; LOE = level of evidence; LOT-R = Revised Life Orientation Test; OD = olfactory dysfunction; PIOD = postinfectious olfactory dysfunction; PTOD = posttraumatic olfactory dysfunction; QOD = Questionnaire of Olfactory Disorders; QOD-NS = Questionnaire of Olfactory Disorders-Negative Statements; QOL = quality of life; S&T = smell and taste; SF-8 = 8-Item Short Form Health Survey; SF-36 = 36-Item Short Form Health Survey; SNOT-22 = 22-item Sino-Nasal Outcome Test; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; SWLS =Satisfaction with Life Scale; TDI = threshold, discrimination, and identification; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

take into account scale differences and test reliabilities, as described elsewhere.[1240] 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 (eg, magnitude estimation) are not recommended as sole measures of smell function largely because of their dependence on stimulus range,[1241] susceptibility to context effects,[1242] lack of normative data, susceptibility to memory factors,[1243] and lesser sensitivity to OD associated with age[1244] and a number of diseases (eg, schizophrenia[1245]). Although there are proponents of magnitude estimation (eg, 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.[1246] However, such scales have inherent limitations that most likely impact the comparison of their results between individuals.[1247]

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 noncommercial 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

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

Study	Year	LOE	Study design	Study groups	Primary end point	Conclusions
Henkin et al[1434]	2013	4	Observational (cross-sectional)	Control: 9 patients with normosmia Hyposmia group: 59 patients 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 with controls	Overall, IL-6 levels in hyposmic patients significantly higher than controls in plasma, saliva, and nasal mucus By etiology: Plasma: all causes of hyposmia with significantly higher concentrations of IL-6 compared with controls Urine: Only congenital hyposmia with reduced concentration of IL-6 compared with controls Saliva: Only head injury and burning mouth syndrome cause of hyposmia with significantly higher concentration of IL-6 compared with controls Nasal mucus: Only postinfluenza hyposmia and burning mouth syndrome causes with significantly higher concentrations of IL-6 compared with controls
Schubert et al[1435]	2015	3	Individual cohort	1611 patients from EHLS	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 OD
Schlosser et al[1427]	2016	4	Observational (cross-sectional)	CRSsNP: 19 patients CRSwNP: 15 patients	Correlation of olfactory mucus cytokine concentration to SS-TDI	Significant correlations of mucus protein concentration to TDI score CRSsNP Negative correlation: IL-5 Positive correlation: None CRSwNP Negative correlation: IL-5 Positive correlation: IL-6, IL-7, VEGF-A

(Continues)

TABLE VIII.12 (Continued)

Study	Year	LOE	Study design	Study groups	Primary end point	Conclusions
Lavin et al[1428]	2017	4	Observational (cross-sectional)	Controls: 26 patients CRSsNP: 37 patients CRSwNP: 36 patients	Correlation of eosinophilic cationic protein with CLC protein CLC protein correlation with IL-5 and CCL11/eotaxin 1 Correlation with CLC protein SS-T and UPSIT®	Significant strong negative correlation between ECP and CLC protein in all patients Significant moderate positive correlation 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[1429]	2018	4	Observational (cross-sectional)	Control: 12 patients CRSsNP: 31 patients CRSwNP: 36 patients	Correlation of olfactory mucus cytokine concentration to UPSIT®	Significant correlations of mucus protein concentration to UPSIT® score 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[1430]	2019	4	Observational (cross-sectional)	CRS: 110 patients	Association of olfactory mucus cytokine concentrations to UPSIT® using cluster analysis and random forest algorithm to examine cytokines most predictive of UPSIT® score	Univariate regression analysis Increased concentrations of IL-2, IL-5, and IL-13 significantly associated with OD Multivariate regression analysis Increased concentration of IL-2 significantly associated with OD Random forest approach IL-5 and IL-13 with most predictive of OF in CRS
Yoo et al[1436]	2019	4	Observational (cross-sectional)	Non-CRS: 34 patients Normosmic: 12 patients Hyposmic/anosmic: 22 patients	Correlation of olfactory mucus cytokine and select protein concentrations to SS-TDI score	Significant correlations of mucus protein concentration to TDI score Negative correlation: CDKN2A/p16INK4a, basic fibroblast growth factor, CCL2, GM-CSF, CCL20 Positive correlation: stem cell factor

(Continues)

TABLE VIII.12 (Continued)

Study	Year	LOE	Study design	Study groups	Primary end point	Conclusions
Soler et al[1431]	2020	4	Observational (cross-sectional)	CRSsNP: 25 patients CRSwNP: 37 patients	Correlation of olfactory mucus cytokine concentration to SS-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, and CCL11 Positive correlation: none
Darnell et al[1433]	2020	3	Individual cohort	2084 patients from NSHAP	Association of plasma cytokine concentration profiles with OD 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[1432]	2020	4	Observational (cross-sectional)	CRSsNP: 25 patients CRSwNP: 46 patients	Correlation of olfactory mucus cytokine concentration to SS-TDI score	Significant correlations of mucus protein concentration to TDI score CRSsNP Negative correlation: TNF-α, IL-10 Positive correlation: none CRSwNP Negative correlation: IL-4 and IL-5 Positive correlation: none

CDKN2A = cyclin-dependent kinase inhibitor 2A; CCL = chemokine (C-C motif) ligand; CLC = Charcot-Leyden crystal; CRP = C-reactive protein; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; CXCL5 = chemokine (C-X-C motif) ligand 5; ECP = eosinophil cationic protein; EHLS = Epidemiology of Hearing Loss Study; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; LOE = level of evidence; NSHAP = National Social Life, Health, and Aging Project; OD = olfactory dysfunction; SS-T = Sniffin' Sticks threshold only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, and identification; TNF-α, tumor necrosis factor α; VEGF-A = vascular endothelial growth factor A.

*For psychophysical testing (University of Pennsylvania Smell Identification Test [UPSIT®], threshold, discrimination, and identification [TDI] score, UPSIT®, San Diego Odor Identification Test [SDOIT], and Olfactory Function Field Exam [OFFE]): higher score indicates better olfactory function (OF).

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

encouraged for research studies in which subtle effects are expected or cultural factors may impact study outcomes.

D | Use of validated survey QOL testing

Olfactory-specific QOL can be assessed by multiple methods including survey responses, symptom scores, and VAS.[1380] Often, these patient-reported methods supplement quantitative olfactory testing. Several instruments have been described and validated, including the Questionnaire of Olfactory Disorders (QOD),[1381] the Assessment of Self-Reported Olfactory Function and Olfaction-Related QOL (ASOF),[1382] the Multi-Clinic Smell and Taste Questionnaire-Scandanavian (MCSTQ-Sc),[1383] and other QOL-based surveys.[1384] These surveys generally provide information regarding the degree to which patients experience OD. The QOD is the most commonly used metric, of which the most frequently employed version incorporates 17 negative statements (QOD-NS).[1380] The QOD has high consistency, reliability, and validity.[1380] Thresholds of clinical relevance exist for this instrument.[1385]

Beyond validated questionnaires, nonvalidated 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 22-item Sino-Nasal Outcome Test (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 patients with CRS identified a moderate correlation between QOD and 40-question Smell Identification Test findings ($r = 0.40$).[1390] OD identified via the SS test is associated with worse QOD-NS scores among patients with CRS, with receiver operating characteristic analysis yielding a sensitivity of 60.9% and specificity of 81.8% for the QOD-NS to detect quantitative OD.[1391] Alternatively, after medical treatment of CRS, improvement in SS was not associated with QOD-NS scores ($r = -0.016$) on short-term follow-up.[1392] In a community-based sample of 7267 individuals, negligible associations were identified between SS results and general health QOL surveys.[1393] However, other studies in dysosmic adults and in patients with PIOD, PTOD, sinonasal OD, and IOD show that QOD scores were generally associated with SS findings.[1394,1395]

Among patients with CRS, olfactory-specific QOL is further impaired in patients with NPs and comorbid allergy.[1390,1396] Deficits on the QOD-NS have been associated with worse economic and productivity metrics in patients with CRS.[1397] Patients who underwent both surgical and medical treatment of CRS have reported improvements in QOD-NS scores.[1390,1392,1396]

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 nonvalidated questionnaires when assessing patient-reported OD, although 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 OF.[1398] An international series employed the QOD along with VAS and concluded that olfactory or gustatory dysfunction may represent early symptoms of infection.[1399] A series of patients with mild COVID-19 infection demonstrated elevated QOD scores, which correlated with impaired psychophysical olfactory testing and gustatory dysfunction.[1400]

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.[1394] Patients with anosmia and hyposmia had impairments on the MCSTQ-Sc.[1401] A multinational study of patients from smell and taste clinics demonstrated that those with postinfection OD and PTOD had worse olfactory-specific QOL than those with sinonasal and IOD.[1395]

The impact of OD is broad and extends beyond olfactory-specific realms. Patients with OD often describe anhedonia, frustration, sadness, and isolation.[1402] In addition to olfactory-specific QOL deficits, individuals with OD from both CRS and non-CRS causes have impairments in areas including general health-related QOL, depression, loneliness, and productivity loss.[1394,1396,1397]

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

Aggregate grade of evidence: C (Level 3: nine studies; Level 4: three studies).

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 nonuse 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 with the healthy population.

Policy level: Use of a validated QOL survey is recommended in individuals with OD related to CRS.

Use of a 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.

E | Measurement of cytokine/mucin levels

Olfaction requires odorant molecules to reach the OE, receptor binding, signal transduction and transmission, and interpretation in the CNS. Thus, any pathology in this process can result in loss of olfaction, leading to many potential causes for OD. Inflammatory sinonasal disease, such as CRS, is the most common cause of olfactory loss, and it appears that many factors including local inflammation-mediated OE injury, nasal obstruction, and OC binding protein and mucous transport abnormalities, among others, may be involved in OD in CRS.[1403] 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 OE.

Lane et al utilized a mouse model of reversible TNF-α mediated inflammatory infiltration and found thinning of the OE with atrophy of axon bundles in the neural layer, and severely diminished electro-olfactogram (EOG) responses.[1404] TNF-α may also affect OE regeneration, and downstream cytokines may play a role in inflammatory OD.[1405–1408] Other murine studies have implicated IL-4, IL-5, IL-13, IL-17c, chemokine (C-C motif) ligand (CCL) 28, and chemokine (C-C motif) receptor 5 in OD.[1409–1412]

Six studies of human CRS-related dysosmia have correlated psychophysical olfaction to OE biopsy or olfactory mucus samples.[1413–1418] 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 5, while olfaction in CRSwNP was inversely correlated with TNF-α, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, CCL2, CCL5, and CCL11 and directly correlated with IL-6, IL-7, and vascular endothelial growth factor A.[1413,1415,1417,1418] Two other studies utilizing hierarchical cluster analysis and OE tissue biopsies found associations between IL-2, IL-5, IL-13, and CCL11 and olfaction.[1414,1416] Only the inverse correlations of IL-5, IL-6, IL-10, IL-13, and CCL11 to olfaction in CRSwNP were found in multiple studies, with IL-6 also showing a direct correlation in one study.[1413,1415,1417,1418]

Four studies have evaluated inflammatory proteins in non–CRS-related OD.[1419–20] Schubert et al[1421] found no associations between baseline systemic C-reactive protein, IL-6, and TNF-α to subsequent development of OD over 10 years and Darnell et al[1419] 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. Henkin et al[1420] found that IL-6 levels were significantly higher in the plasma, saliva, and nasal mucus of hyposmic patients compared with normosmic patients. Yoo et al[20] evaluated OC 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, CCL2, CCL20, and granulocyte-macrophage colony-stimulating factor, and a direct correlation with stem cell factor. Notably, the results from non-CRS studies were largely dissimilar to the findings from the CRS studies, pointing to the likelihood that OD in CRS-related and non-CRS–related causes 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 OF, but only a few cytokines (IL-5, IL-6, IL-10, IL-13, and CCL11) have shown reproducibility of the associations among multiple studies. This variability is likely attributable to the heterogeneity of etiology of OD. Although promising as a way to identify potential therapeutic targets and/or strategies, further investigation is required to transform this potential into a clinical tool.

Multiple nasal mucus proteins have been associated with OF, with a few cytokines showing reproducibility of association with OF among multiple human and murine studies (IL-5, IL-6, IL-10, IL-13, and CCL11).

Some of the inconsistency in findings are likely related to the heterogeneity of causes of OD and further study into these associations is required.

Aggregate grade of evidence: C (majority of observational studies with variable results, Level 3: two studies; Level 4: eight studies).

F | Electro-olfactogram

The EOG is an electrophysiological equivalent of olfactory activation at the level of the olfactory mucosa. It represents the summated generator potentials of OSNs in response to an olfactory stimulus. While this measurement technique has been used extensively in animal research since

TABLE VIII.13 Diagnostic use of the EOG

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Furukawa et al[1452]	1989	4	Observational	Patients with olfactory loss (n = 34)	Presence of EOG response	Patients with "peripheral" cause of olfactory loss have fewer responses than those with "central" loss The number of EOG responses increases with increasing OF
Turetsky et al[1453]	2009	3	Observational	Patients with schizophreia (n = 21) HCs (n = 18))	EOG amplitude	Larger EOG amplitudes in schizophrenic patients compared with controls
Hummel et al[1454]	2018	3	Observational	Patients with idiopathic and postinfectious olfactory loss (n = 38) HCs (n = 27)	Presence of EOG response	Patients with olfactory loss have less EOG responses than HCs Normosmic patients have more EOG responses than hyperosmic or anosmic participants Following OT in patients the number of EOG responses increased

EOG = electro-olfactogram; HC = healthy control; LOE = level of evidence; OF = olfactory function; OT = olfactory training.

the 1930s,[1422,1423] its use in human olfaction research has been limited.

Although pioneering work was performed in the 1960s[1424] to 1980s,[1425] EOG research never arrived in routine clinical assessment probably because of the requirements for sophisticated constant-flow olfactometry,[1425] nasal endoscopy,[1426] and the relatively low response yield of ≈50% to 70% with high interindividual variability and low intraindividual variability.[1427–1430]

Among other results, EOGs have been used to provide evidence for the dominant role of the CNS in olfactory desensitization. Specifically, repeated stimulation at short interstimulus intervals produce responses with little or no decrease in amplitude, although simultaneously recorded, electroencephalography-derived olfactory ERPs exhibit such a decrease in amplitudes and intensity ratings decrease.[1425,1431] Leopold et al[1432] used EOGs to functionally describe the extent of the OE.[1432] They reported the presence of EOG responses and functionally mature OSNs at the insertion level of the middle turbinate. Some EOG work also suggested the existence of a specific topographical distribution of ORs with some recording sites only responding to certain odors,[1426] and that the EOG was odorant specific[1427] (and even specific for odorous enantiomers[1433]). 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.[1428] 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 OR hOR17-4. Its antagonist undecanal decreases EOG response amplitudes and intensity of bourgeonal following brief exposure to undecanal.[1434] In addition, EOG recordings suggested that individuals who perceived large differences among odorants also had large EOG differences among odorants.[1428] More recent work utilized EOG responses to display 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.[1435] Similarly, using EOG recordings it was possibly to show that the decreased intensity from retronasally presented odors compared with orthonasal presentation may start at the periphery.[1436]

When focusing on the clinical utility of EOG recordings, a literature search produced 17 results. After careful reading of abstracts, only three 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 patients with OD, suggesting that olfactory disorders are accompanied by a change at the level of the olfactory mucosa.[1437,1439] In addition, OT was associated with a significant increase in the number of EOG recordings in response to odors, suggesting improvement in OF with training.[1439]

Overall, EOG measurements provide an opportunity to record objective neuronal input from the peripheral olfactory system, while simultaneously obtaining

TABLE VIII.14 Role of bloodwork in routine workup of OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Derin et al	2016	3	Retrospective, case-control	39 patients with low vitamin B12 levels 34 controls	SS test	"OD may be present in patients with vitamin B12 deficiency" Negative correlation of age with odor identification score

LOE = level of evidence; OD = olfactory dysfunction; SS = Sniffin' Sticks.

psychophysical responses in awake humans.[1440] However, similar to other measures of chemosensory activation at the nasal mucosa,[1441,21] the evidence level of EOG-related studies in a clinical context is currently low.

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

Aggregate grade of evidence: C (Level 3 studies: two; Level 4 studies: one).

G | Role of bloodwork/lab values

The literature on laboratory studies for evaluation and diagnosis of OD is sparse. This is likely why many previous position papers, such as the 2017 Position Paper on Olfactory Dysfunction,[1441] 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 that are associated with OD.

Derin et al[1442] shed light on the role of vitamin B12 in OD. 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 patients in the control group had OD, 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 OD,[1443] 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.[1444,1445] Moreover, zinc nutritional status is difficult to adequately measure using laboratory tests.[1446] 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,[1447] bearing in mind that anosmia has been associated with the use of zinc-containing nasal gels or sprays, leading to a warning by the US Food and Drug Administraion (FDA) in June 2009. These products have since been taken off the market.[1448]

Both hypogonadotropic hypogonadism, ie, 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[1449] showed that 56% had a family history of either anosmia or infertility. Laboratory diagnosis is based on a constellation of low serum levels of testosterone, luteinizing hormone, and follicle-stimulating hormone.[1449–1452] 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.[1450] With genetic testing becoming more readily available, this will also be an avenue of laboratory investigation performed by specialist services.

Various neurologic conditions can present with loss of sense of smell, such as PD and AD.[1453] Although no blood tests exist for PD at present, a promising blood test for AD has been recently developed.[1454] When dealing with other causes of OD, eg, toxins, such as heavy metals or lead,[1455] Sjögren syndrome,[1456] DM,[1457] Wilson disease,[1458] and liver cirrhosis,[1459] 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 caused by 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.[1460–1462] More importantly, COVID-19 represents one of the only causes of PVOL for which antibody testing could become a standard of care as part of the diagnostic workup, taking into account preliminary data obtained so far.[1463,1464]

In summary, evidence-based literature on laboratory studies for evaluation and diagnosis of OD is 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 OD. Until then, thorough history-taking, review of systems, and knowledge of the various causes of OD are still required to guide the physician on a case-by-case basis.

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

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

H | 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.[1465] 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.[1465,1466] Patients will often describe phantom smells as smoky, burned, foul, unpleasant, spoiled, or rotten.[1465–1467] 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.[1465–1469]

In contrast to other qualitative olfactory disorders, most cases of phantosmia are idiopathic and less commonly present after URI, head injury, or with aging.[1465,1469,1470] There are several neurologic and psychiatric disorders that have been shown to be associated with phantom smells including temporal lobe epilepsy, migraine disorder, PD, intracranial neoplasm, depression, schizophrenia, and olfactory reference syndrome. Other reported associations include CRS, iatrogenic causes, and metabolic disorders.[1465,1467,1469,1471–1478] The exact mechanism is unknown with each of these potential causes, but both peripheral and central triggers have been hypothesized.[1465,1466,1468,1471,1477,1479] Certainly, olfactory processing in the CNS 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 OC and 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 whether it is unilateral or bilateral.[1465,1466,1480,1481] 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.[1472,1480,1481]

Although phantosmia has been shown to be associated with a decrease in quantitative OF in the affected nostril(s), this is not always the case.[1469,1471,1472] Nevertheless, uninasal olfactory testing (identification and possibly threshold testing) should be performed to document the patient's baseline OF at initial evaluation.[1465,1466,1472,1480,1481]

Imaging should include a CT scan of the head/sinuses and/or MRI of the brain to rule out intracranial or sinonasal pathology.[1465,1483,1497,1498] Electroencephalography, positron emission tomography, and fMRI are generally reserved for research purposes and not recommended for the initial workup of phantosmia.[1483,1498] Laboratory studies are not needed in the workup of phantosmia. Appropriate referrals to neurology, psychiatry, or endocrinology for further evaluation and/or treatment should be considered.

IX | MANAGEMENT

A | Prognosis and spontaneous recovery

Estimating true spontaneous recovery time after the onset of OD is difficult, as many patients delay reporting smell loss. This makes it difficult to establish a 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 among studies, leading to many discrepancies in recovery data. For instance, removing studies with subjective measures,[1482–1484] smell loss from head injury is related to slower and lower recovery rates (0%–44%) than postviral loss (0%–77 %).[1485–1494] 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.[1488,1489,1492,1495,1496] Interestingly, COVID-19, a disease that attacks the underlying structure or supporting cells,[1497] 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.[1498–1501] OSNs do not express the necessary viral entry gene ACE2 for COVID-19 infection, unlike supporting cells underlying the OE (eg, sustentacular or microvillar cells). These cells manage epithelial maintenance through delivery of glucose to 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 OE (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 OE to reacquire a population of neurons similar to a healthy state.[1502] 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,[1489–1491,1493,1503] others showed no effect with duration of loss.[1486,1488,1504] 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.[1483,1484,1505] However, even after recovery, a portion of patients will still experience parosmia or a distorted sense of smell[1492,1506,1507,1508] and phantosmia,[1509] presumably caused by altered olfactory receptor neurons and their retargeting of glomeruli in the OB or onward at the level of the cortex.[1502,1510,1511]

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 among multiple studies.[1488,1489,1491,1493,1504] However, a lack of correlation has also been reported.[1490,1503,1512,1513] Decreased recovery may be caused by a reduced regenerative capacity of OSNs that comes with advancing age.[1514] In parallel, the size of the OE decreases with age and there may be more respiratory metaplasia over years of insult from diseases in which the damaged OE is replaced by respiratory epithelium and no longer functions as a sensory organ.[1514,1515] This can be seen in mice in which telomere shortening (a basic mechanism of cellular aging) impairs OE regeneration, but not homeostatic conditions.[1516] 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 OB and other important processing areas, may lead to less efficient central recovery.[1514,1515,36] There may also be a sex influence, with some reports showing females recovering more often than males[1486,1488–1490]; however, again, many reports have shown no difference[1491,1493,1503,1504,1513] (Tables IX.1-X1.2). Last, although most studies show no link between parosmia at initial diagnosis and better olfactory recovery,[1488] this has been postulated as a potential predictive sign.[1492]

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

Aggregate grade of evidence: C (Level 2: three studies; Level 3: three studies; Level 4: 11 studies; Level 5: one 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.

TABLE IX.1 Prognosis and spontaneous recovery

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Sumner[1500]	1964	4	Case series (within a year; 2 to 16 years)	1167 patients 101 patients with PTOD (series)	Δ Subjective: unknown	39% of patients with PTOD recovered at varied time but typically within 10 weeks except in rare cases (5 years for one)
Zusho[1501]	1982	4*	Retrospective cohort (across 15 years)	56 patients with PTOD	Δ Subjective: unknown	14% of patients with PTOD recovered at varied times (case study with 7 years)
Deems et al[1502]	1991	4*	Retrospective cohort (5 months to 6 years)	306 patients with OD	Δ UPSIT®	No recovery for patients with PTOD and and those with PVOD, but some recovery for those with RS No percentages given
Doty et al[1503]	1997	4	Case series (1 months to 13 years)	248 patients with PTOD 66 patients with PTOD (series)	Δ UPSIT® Δ Questionaire	36% showed improvement, but this, along with duration, was not significant Change with age modeled, but not reported
Mori et al[1507]	1998	4*	Retrospective cohort (2 months to unknown)	889 patients with OD	Δ T&T olfactometer	Improvement by etiology (AR>RS>PVOD>PTOD) Longer duration of disorder and sex (male) lead to worse prognosis in patients with PTOD and those with RS, but not in patients with PVOD No effect of age on prognosis
Hummel et al[1513]	1998	2	RCT (0, 2, 4, 6, and 35 days)	12 AR controls 2) 12 patients with AR with oxymetazoline (0.25 mg/mL) 12 patients with AR with oxymetazoline (0.5 mg/mL)	Δ Subjective sypmtoms SS-TDI Δ Rhinometry Δ csERPs	Within a month, olfactory outcomes increased from day 0 to 35 Congestion dependency was found in some, but not all, outcomes
Reden et al[1510]	2006	3	Retrospective cohort (1 to 216 months)	262 patients with PVOD 99 patients with PTOD	SS-TDI	32% of patients with PVOD and 10% of patients with PTOD improved in olfactory Age was negatively associated with improvement
Reden et al[1509]	2007	4*	Retrospective cohort (no range given; mean 11 months)	392 patients with OD	Δ SS-TDI	Improvement by etiology (RS/AR [31%] >PVOD (27%) >PTOD/idiopathic [18%]) Patients with PVOD had more parosmia, but this did not impact recovery
London et al[1506]	2008	3	Retrospective cohort (3 to 283 months)	542 patients with OD	Δ UPSIT®	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

(Continues)

TABLE IX.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Mueller and Hummel[1522]	2009	5*	Case report	1 patients with PTOD	SS-TDI csERPs	Patient recovered after 9 years of subjective loss
Rombaux et al[1530]	2010	4	Case series (4 to 18 months)	27 patients with PVOD	Δ SS-TDI Δ csERPs Δ Retronasal 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[1505]	2010	4*	Retrospective cohort (1 to 106 months)	463 PVOD 220 AR/RS 211 PTOD	Δ SS-TDI	Improvement by etiology (RS/AR [76%] >PVOD [46%] >PTOD [44%]) Lower age, increased parosmia, and sex (female) had increased recovery rates
Rombaux et al[1511]	2012	4	Case series (no range; mean 14.6 months)	28 patients with PVOD 32 patients with PTOD	Δ SS-TDI Δ OBV Δ Retronasal ID	36% of patients with PVOD and 25% of patients with PTOD improved in olfactory Larger bulbs related to better recovery
Lee et al[1499]	2014	4	Case series (mean 33 months)	63 patients with PVOD 20 controls	Δ Subjective: VAS, binary Δ BTT (n = 25)	86% reported subjective improvement and unknown for threshold testing
Brann and Firestein[1534]	2014	1	Review	NA	NA	Mechansims underlying neurogenesis in the subgranular zone, the subventiricular zone, and OE
Mobley et al[1531]	2014	1	Review	NA	NA	Mechanisms underlying olfactory neurogenesis with age
Doty[1532]	2014	1	Review	NA	NA	Age-related declines in olfactory ability along with regeneration decreases
Fan et al[1529]	2015	3	Retrospective cohort (1 to 52 months)	107 patients with PTOD	Δ UPSIT®	16.8% recovered and no prognosis factors were relevant to recovery
Konstantinidis et al[1520]	2016	2	RCT (0, 8, 16, 25, 32, 40, 48, and 56 weeks)	41 patients with PVOD 36-short OT 34-long OT	Δ SS-TDI	37% of PVOD control improved For controls, duration of olfactory loss, but not age or sex, was related to improvement
Schwob et al[1519]	2017	1	Review	NA	NA	Horizontal basal cells contribute to OE damage and mechanisms are discussed
Hummel et al[1535]	2017	1	Review	NA	NA	List of interventions that have an impact on olfactory loss recovery
Pellegrino et al[1512]	2017	3	Prospective cohort (21 to 90 days)	57 RS controls	Δ SS-TDI Δ Retronasal ID Δ Rhinometry	Smell (and nasal dimensions) decreased during RS, but almost all patients improved on recovery No imporovement in retronsasal smell

(Continues)

TABLE IX.1 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Cavazzana et al[1521]	2018	4*	Retrospective cohort (mean 1.94 years)	791 postviral patients	Δ SS-TDI	Age and severity were important prognostic factors.
Ogawa et al[1508]	2020	2*	Retrospective cohort (0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 36, 39, and 42 months)	82 patients with PVOD	Δ T&T olfactometer	77% of patients showed recovery, with 60% recovering within 6 months Lower age and more residual function, but not sex, lead to higher recovery rates

Δ = change; AR = allergic rhinitis; BTT = Butanol Threshold Test; csERP = chemosensory functions with event-related potential; ID = identification; NA = not available; OBV = olfactory bulb volume; OD = olfactory dysfunction; OE = olfactory epithelium; OT = olfactory training; PTOD = posttraumatic olfactory dysfunction; PVOD = postviral olfactory dysfunction; RCT = randomized controlled trial; RS = rhinosinusitis; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.
*Ranked down a level of evidence (LOE) because of methodological concerns.

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 (eg, 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 (eg, restrict to loss no longer than 1 year).

B | Treatment of posttraumatic loss

While spontaneous recovery has been observed following some cases of posttraumatic olfactory loss,[1516] several studies have investigated treatment with medications. One study reported that spontaneous improvement rate was only 10% on average after 23 months of observation.[1517] Kampo medicines (Japanese herbal medicine), zinc or vitamin preparations, topical or systemic steroids, and adenosine triphosphate have been used to treat PTOD. Some recent reports indicate that OT is also effective in recovering OF.[1518]

From Kampo medicine, Toki-shakuyaku-san (TSS) treatment improved OF in 42% of patients with PTOD.[1519] In another study, seven patients with PTOD were treated with kamikihito. In this study, one patient recovered, five patients improved, and one patient showed no change.[1520]

For zinc, although a prior double-blind, crossover study of 106 patients found no statistically significant effects on either taste or smell after 3 to 4 months of treatment,[1521] 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.[1522] In another study, 95 patients with PTOD 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.[1523] Another study reported that 22 patients with PTOD were treated with zinc sulfate, TSS, and vitamin B_{12} complex, and five patients were cured, five patients improved, 10 patients showed no change, and two patients showed an exacerbation of symptoms.[1524]

For steroids, some case studies have reported the efficacy of topical or systemic steroids. A total of 108 patients with PTOD were treated with topical steroids, and the improvement rate was 25%.[1525] In another study, 12 patients with PTOD were treated with topical betamethasone, with only one of 12 patients showing an improvement in the olfactory test score. Five patients were also treated with topical dexamethasone, and three of the five patients showed an improvement.[1526]. In another study, 116 patients with PTOD 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.[1527] Patients with PTOD 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 TSS was compared, but no significant differences were observed.[1519]

For vitamin A, in a double-blinded, placebo-controlled study, a dose of 10,000 IU/day was administered to 52 patients with olfactory loss, including 19 patients with posttraumatic olfactory loss, for 3 months. No significant

improvement (as evaluated by the SS olfactory test) was observed 5 months after the initial test.[1528]

A prospective study with 38 patients with PTOD was performed to investigate the effect of OT.[1518] The training group underwent OT for 5 minutes twice daily using the following four odorants: phenylethyl alcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves). Compared with the control group, the training group had significantly higher OF scores, as measured by the SS test at 16 weeks. The improvement rates of both groups were 33% and 13%, respectively. In another study 16 of 52 patients responded to OT. The authors found factors including the absence of a cribriform plate fracture, absence of OB encephalomalacia or siderosis, deep olfactory fossa (>4.9 mm), and larger OBVs (>27.1 mm^3) were related to a better prognosis.[1529] OT has also been reported to be more effective in improving olfactory threshold scores in anosmic patients and in improving identification scores in hyposmic patients.[1530]

No RCTs have been performed evaluating any of these interventions on only a posttraumatic olfactory loss group. In order to fully investigate the efficacy of a medication or other intervention, it is necessary to conduct RCTs and evaluate therapeutic interventions at an early stage after injury. With the existing data, OT 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, because of the limited efficacy of treatment options for PTOD, patient counseling about hazardous events and safety issues is helpful since persistent OD results in a higher level of disability and lower QOL.[1531]

Treatment of PTOD.

Aggregate grade of evidence: C (Level 1: one study; Level 2: two studies; Level 3: one study; Level 4: nine studies).

Benefit: OT may be effective in limited patients with posttraumatic dysfunction. Oral steroids, Kampo, and oral zinc medications may also benefit these patients, although the data are not as robust to support this.

Harm: High-dose steroids may induce systemic adverse effects. Some Kampo medications can elevate liver function levels.

Cost: Expense for comparatively prolonged use of medication to restore OT. OT is very inexpensive.

Benefits-harm assessment: Beneficial to less than half of patients with PTOD with few side effects.

Value judgments: It is worth trying treatment for PTOD at an early stage after injury.

Policy level: Use of OT is recommended in patients with PTOD.

Use of oral steroids, Kampo, and zinc medications are options in patients with PTOD.

Intervention: OT should be considered in patients with PTOD.

C | Treatment of underlying sinonasal inflammatory etiologies

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

OD affects a significant portion of the general population, with some reports estimating it to be as high as 24%.[1536] Inflammatory nasal pathologies such as CRS and AR are the most common forms of acquired OD, particularly in younger populations worldwide.[1537] Smell loss in CRS is likely caused by a combination of factors that either inhibits odorant transport to the OC and/or odorant transduction at the level of the olfactory neuroepithelium. These inflammatory changes may also lead to degeneration of the OE, further causing a reduction in smell.[1538] 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.[1539] 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 nonolfactory benefits that these medications may confer in patients with CRS or AR.

The majority of clinical studies investigating olfactory outcomes include subjective assessments and/or olfactory psychophysical tests. Subjective assessments include measures such as olfaction specific VAS, subjective symptom scores, and QOL questionnaires (eg, 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 UPSIT®, SS test, Barcelona Smell Test (BAST), and Butanol Threshold Test (BTT).[1540] As evident in the accompanying tables, the treatment of OD in patients with CRSwNP has been studied to a greater degree compared to that in patients with CRSsNP or AR. This is likely secondary to the greater severity and higher prevalence of OD in patients with CRSwNP.[1541]

In CRSwNP, there is grade A evidence composed of RCTs demonstrating that oral steroids and some biologics improve subjective and psychophysical metrics of OD.[1542–1546] Topical steroids also appear to improve OF based on grade A evidence, but most studies demonstrate a benefit in subjective metrics only and more studies

TABLE IX.2 Section evidence summary: Management of PTOD

Study	Year	LOE	Design	Study groups	Clinical end point	Conclusions
Reden	2006	4	Retrospective	99 patients with PTOD Observation	SS-TDI outcomes: 10% improved, 83% no change 7% worsened	Spontaneous improvement rate of posttraumatic olfactory loss was poor
Konstantinidis	2013	3	Prospective	38 patients with PTOD 23 of 38 patients with OT for 16 weeks 15 ot 38 control patients	SS-TDI outcomes: 33% of patients with OT and 13% of controls improved	OT is useful for treatment of PTOD
Miwa	2005	4	Retrospective	PTOD TSS vs topical steroids	T&T olfactometer outcomes: 41.7% improved by TSS 28.8% improved by Kamikihito	No significant difference in improvement rates between TSS and topical steroids
Shiga	2014	4	Retrospective	13 patients with PTOD 6 of 13 TSS 7 of 13 Kamikihito	T&T olfactometer outcomes: 2 of 6 (33%) improved by TSS and 6 of 7 (86%) by Kamikihito	Kamikihito is useful for treatment of posttraumatic dysfunction
Jiang	2015	2	Prospective	145 patients with PTOD 39 of 145 zinc gluconate for month and prednisolone for 2 weeks 35 of 145 zinc gluconate only 34 of 145 prednisolone only 37 of 145 no medication	PEA threshold outcomes: 11 of 39 (28%) improved by zinc gluconate and prednisolone 9 of 35 (26%) zinc gluconate only 4 of 34 (12%) prednisolone only 1 of 37 (3%) no medication	Zinc gluconate has a promising effect in treating posttraumatic anosmia
Aiba	1998	4	Retrospective	95 patients with PTOD 4 of 95 zinc sulfate 300 mg/day 70 of 95 topical corticosteroids and systemic vitamin B complex 21 of 95 zinc sulfate and the complex	T&T olfactometer outcomes: 2 of 4 (50%) improved with zinc sulfate 11 of 70 (43%) by steroids and systemic vitamin B complex 9 of 21 (16%) by zinc sulfate and the complex measured by patients' self-reported scores	Zinc sulfate is significantly more effective than steroids and systemic vitamin B complex against PTOD
Kitano	2013	4	Retrospective	57 patients with PTOD	T&T olfactometer and intravenous olfactory test (Alinamin test) results: 45% improvement rate	Positive responders on olfactory tests at the first visit get better recovery of OF than nonresponders
Mori	1998	4	Retrospective	108 patients with PTOD Topical corticosteroids	T&T olfactometer and intravenous olfactory test (Alinamin test) results: 25% of improvement rate by patients' self-reported scores	Patients with PTOD treated with topical steroids had poor recovery and prognosis

(Continues)

TABLE IX.2 (Continued)

Study	Year	LOE	Design	Study groups	Clinical end point	Conclusions
Ikeda	1995	4	Retrospective	17 patients with PTOD 12 of 17 topical nasal drop of 0.1% betamethasone 5 of 12 oral administration of prednisolone	T&T olfactometer outcomes: 1 of 12 (8%) improved by topical betamethasone 3 of 5 (60%) improved by oral prednisolone	Corticosteroids may induce regeneration of OR cell axons and reestablishment of contact with cells in the OB
Jiang	2010	4	Retrospective	116 patients with PTOD Oral prednisolone (60 mg/day for 3 days, tapered every 3 days for 15 days)	PEA threshold outcomes: 16% improved by oral steroids	Oral steroid administration is effective in limited patients with posttraumatic dysfunction
Reden	2012	1	Prospective	19 patients with PTOD 10 of 19 vitamin A 10,000 IU/day oral administration for 3 months 9 of 19 placebo controls	SS-TDI outcomes No significant improvement	Vitamin A is not useful in the treatment of PTOD
Altundag	2021	4	Retrospective	52 patients with PTOD OT	SS-TDI outcomes: 16 of 52 (31%) responders to OT 36 of 52 (69%) nonresponders	Good prognosticators were no cribriform plate fracture, no OB encephalomalacia, no siderosis, deep olfactory fossa, and large OBV
Pellegrino	2019	2	Prospective	42 patients with PTOD 18 of 42 hyposmia 24 of 42 anosmia	SS-TDI outcomes Greater threshold improvement in anosmic patients Better identification ability in hyposmic patients	OT is effective for both anosmia and hyposmia

LOE = level of evidence; OB = olfactory bulb; OR = olfactory receptor; OT = olfactory training; PEA = phenylethyl alcohol; PTOD = posttraumatic olfactory dysfunction; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; TSS = Toki-shakuyaku-san.

looking at psychophysical metrics are needed. Dupilumab and omalizumab have been studied in patients with severe CRSwNP 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.[1547] Oral antibiotics and antileukotriene therapy have been studied with RCTs, but they do not appear to provide clear benefit in regards to olfaction, which therefore precludes their routine use specifically for OD in patients with CRSwNP. In patients with CRSwNP caused by AERD, aspirin desensitization, and daily aspirin therapy may be considered, particularly as an option following sinus surgery. There are few randomized controlled clinical trials investigating aspirin 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 patients with 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 because of systemic side effects. Studied duration of oral steroid treatment in patients with CRSwNP ranges from 1 to 2 weeks with evidence suggesting that there is an initial benefit with return to baseline symptoms within 3 months following treatment.[1548] For biologics, available evidence suggests that subjective and psychophysical scores decline as early as 8 weeks after cessation of therapy.[1543] Assessing the comparative effectiveness of topical steroids, oral steroids, and biologics is challenging because of 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 patients with 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.[1549–1552] Therefore, no recommendation can be made regarding macrolide therapy for OD in patients with CRSsNP refractory to more conservative therapy.

In patients with AR, there are few randomized controlled clinical trials investigating olfactory outcomes. Topical intranasal steroids are recommended for treatment of OD in patients with AR, with some randomized clinical trials demonstrating benefit in objective and subjective assessments of olfaction.[1553–1558] The literature on immunotherapy primarily consists of case series and one RCT, which together demonstrate improvement in subjective and objective olfactory outcomes.[1559–1563] 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 patients with AR.

OD is more common and more severe in patients with CRSwNP compared with patients with CRSsNP or AR.[1539,1541] 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 patients with CRSwNP. There is also support for the use of regular sustained topical steroid use for OD in patients with CRSwNP, but this data are largely in the form of subjective outcomes. Oral steroids are generally used for short durations ranging from 1 to 3 weeks and topical intranasal steroids are used for sustained longer-term use. Biologics are used for prolonged periods at regular intervals (every 1 to 4 weeks), they do not all have the same effect on OD, and olfactory benefit is unknown once the medication is stopped. These medications are recommended for the treatment of OD in patients with CRSwNP in the appropriate clinical circumstances. Further high-level studies investigating use of medical therapy for treatment of OD are needed, especially in patients with CRSsNP or AR. (Tables IX.3-17)

Oral corticosteroids for OD in patients with CRSwNP.

Aggregate Quality of Evidence: A (Level 1: one study; Level 2: 11 studies).

Benefit: Significant short-term improvements in subjective and objective measures of olfaction in patients with CRSwNP. Duration of improvement with systemic corticosteroid alone may last 2 to 4 weeks, but this benefit may be lengthened with concurrent use of topical intranasal corticosteroids.

Harm: Corticosteroid risks include gastrointestinal (GI) 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 OD in CRSwNP as part of a shared decision-making approach. Longer-term use of oral steroids for OD in CRSwNP has not been studied and carries increased risk of harm to the patient.

Intranasal topical corticosteroids for OD in patients with CRSwNP.

Aggregate grade of evidence: A (Level 1: two studies; Level 2: 26 studies; Level 3: one study).

Benefit: Significant improvements in subjective and objective measures of olfaction in patients with CRSwNP. 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 OD in patients with CRSwNP.

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

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Ecevit et al[1581]	2015	2	RCT	CRSwNP (N = 22) Oral prednisolone 60 mg × 7 days followed by taper Placebo	VAS (0–10) BTT Data collection points: week 2	Compared with placebo, the prednisone group demonstrated significantly greater improvements in VAS and butanol threshold tests at week 2
Banglawala et al[1558]	2014	1	Systematic review and meta-analysis	CRSwNP (N = 419) 5 RCTs with follow-up ranging 12 to 48 weeks	Subjective olfactory outcomes Objective olfactory outcomes	Compared with placebo groups, the oral steroid groups demonstrated significant improvement in both subjective and objective olfactory outcomes
Alobid et al[1582]	2014	2	RCT	CRSwNP (N = 92) Oral prednisone 30 mg taper × 2 week + budesonide NS 400 μg twice daily × 12 weeks No treatment (n = 22)	BAST-24 Data collection points: week 2 and week 12	Compared with baseline, only the oral prednisone group demonstrated significant improvement at week 2 and week 12
Kirtsreesakul et al[1583]	2012	2	RCT	CRSwNP (N = 114) Oral prednisone 50 mg once daily × 2 weeks followed by MF NS 200 μg twice daily × 10 weeks Placebo once daily × 2 weeks followed by MF NS spray 200 μg twice daily × 10 weeks	Subjective symptom score (0–3) Data collection points: week 12	Compared with baseline, only the oral prednisone group demonstrated significant improvement in subjective symptom score at week 12
Alobid et al[1584]	2012	2	RCT	CRSwNP (N = 62) Oral prednisone 30 mg taper × 2 weeks + budesonide NS 400 μg twice daily × 12 weeks (n = 46) No treatment (n = 16)	Subjective symptom score (0–3) Data collection points: week 2 and week 12	Compared with baseline, neither group demonstrated significant improvement
Vaidyanathan et al[1585]	2011	2	RCT	CRSwNP (N = 60) Oral prednisolone 25 mg once daily × 2 weeks + FP nasal drops 400 μg twice daily × 8 weeks + FP NS × 18 weeks (n = 30) Placebo tablets × 2 weeks + FP nasal drops 400 μg twice daily × 8 weeks + FP NS × 18 weeks (n = 30)	VAS (0–100) PST (0–3) Data collection points: week 2, week 10, week 28	Compared with placebo, the oral prednisolone group demonstrated significantly greater mean improvement in VAS (week 2 only) and PST (week 2 and week 10)

(Continues)

TABLE IX-3 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Van Zele et al[1586]	2010	2	RCT	CRSwNP (N = 47) Oral methylprednisolone 32 mg taper × 20 days (n = 14) Placebo × 20 days (n = 19)	VAS (0–10) Data collection points: week 1, week 2, week 4, week 8, week 12	Compared with placebo, the methyl prednisolone group demonstrated significantly greater improvement in VAS at week 1, week 2, and week 4
Benitez et al[1587]	2006	2	RCT	CRSwNP (N = 84) Oral prednisone 30 mg once daily taper × 2 weeks + budesonide 400 μg twice daily × 10 weeks (n = 63) No treatment (n = 21)	Subjective symptom score (0–3) Data collection points: week 2, week 12	Compared with baseline, only the oral prednisone group demonstrated a significant improvement in subjective symptom score at week 2 This was not sustained at week 12
Wright et al[1588]	2007	2	RCT	CRSwNP (N = 26) Oral prednisone 30 mg once daily × 14 days + ESS (n = 11) Placebo + ESS (n = 15)	VAS (0–10) Data collection points: week 2, week 4, week 12, week 24	Compared with baseline, only the prednisone group demonstrated significant improvement in VAS at week 2
Alobid et al[1589]	2006	2	Controlled clinical	CRSwNP (N = 78) Oral prednisone 30 mg taper × 2 weeks + budesonide 400 μg × 48 weeks (n = 60) No treatment (n = 18)	Subjective symptom score (0–3) Data collection points: week 12, week 24, week 48	Compared with baseline, only the prednisone group demonstrated a significant improvement in subjective symptom score at week 12, week 24, and week 48
Kroflic et al[1590]	2006	2	Randomized comparative	CRSwNP (N = 40) Oral methylpednisolone (1 mg/kg/day) × 7 days (n = 20) Nasal furosemide (6.6 mmol/1 solution) (n = 20)	Subjective symptom score (0–3) Data collection point: week 1	Compared with baseline, subjective symptom scores improved significantly in both the methylprednisolone groups and topical furosemide groups at week 1 No significant difference was seen in values posttreatment when comparing groups
Hissaria et al[1591]	2006	2	RCT	CRSwNP (N = 40) Oral prednisolone 50 mg once daily × 14 days (n = 20) Placebo × 14 days (n = 20)	RSOM-31 (individual smell question) Data collection points: week 2	Compared with baseline, only oral prednisolone group demonstrated significantly improvement in subjective smell at week 2

BAST = Barcelona Smell Test; BTT = Butanol Threshold Test; CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; FP = fluticasone propionate; LOE = level of evidence; MF = mometasone furoate; NS = nasal spray; PST = Pocket Smell Test; RCT = randomized controlled trial; RSOM-31 = 31-item rhinosinusitis outcome measure; VAS = visual analog scale.

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	Conclusions
Xu et al[1592]	2020	2	RCT	CRSwNP (N = 127) Oral methylprednisolone 24 mg once daily + budesonide NS 256 μg once daily (n = 44) Budesonide nasal drops 1 mg once daily and budesonide NS 256 μg once daily (n = 41) Budesonide NS 256 μg once daily (n = 42)	VAS (0–10) Data collection points: week 1	Compared with baseline, all groups demonstrated improvement No significant difference in posttreatment VAS score between groups
Zeng et al[1593]	2019	2	RCT	CRSwNP and CRSsNP (N = 187) FP NS 200 μg once daily Clarithromycin 250 mg once daily	VAS (0–10) Data collection points: month 1, month 3, month 6, month 12	Compared with baseline, both the FP and clarithromycin groups demonstrated significant improvement in VAS but no significant difference between groups
Khan et al[1594]	2019	2	RCT	CRSwNP (N = 310) MF NS 200 μg once daily MF NS 200 μg twice daily Placebo	Subjective symptom score (0–3) Data collection points: month 1 and month 4	Compared with placebo, only the MF NS twice-daily dosing group demonstrated significantly greater improvement at month 1 and month 4
Zhou et al[1595]	2016	2	RCT	CRSwNP (N = 748) MF NS 200 μg twice daily (n = 375) Placebo (n = 373)	Subjective symptom score (0–3) Daily diary Data collection points: week 4, week 8, week 12, week 16	Compared with placebo, the MF NS group demonstrated significantly greater improvement in subjective symptom score at all time points
Chong et al[1596]	2016	1	Systematic review of RCTs	RCTs (n = 18) RCTs of CRSwNP (n = 14) Analysis including dose, frequency, and agent	Subjective measures of olfaction	The quality of the evidence was moderate for sense of smell
Bangwala et al[1558]	2014	1	Systematic review and meta-analysis	A total of 28 RCTs evaluating olfaction in CRSwNP was identified and systematically reviewed	Subjective olfactory outcomes Objective olfactory outcomes	The results of this meta-analysis demonstrated that oral and topical steroids significantly improve olfaction in patients with CRSwNP

(Continues)

TABLE IX-4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Janowski et al[1597]	2009	2	RCT	CRSwNP (N = 246) FP NS 200 μg twice daily × 8 months FP NS 200 μg twice daily × 1 month, followed by FP NS 200 μg once daily + placebo once daily × 7 months Placebo twice daily × 2 months, followed by FP NS 200 μg twice daily for 6 months	VAS (0–100) Mean sense of smell disorder score Data collection points: month 1, month 2, and month 8	Compared with placebo, both FP groups demonstrated significantly greater improvement in VAS (only at month 1) and mean sense of smell disorder score (only month 1 and month 2)
Ehnhage et al[1598]	2009	2	RCT	CRSwNP (N = 68) FP NS 400 μg twice daily Placebo spray twice daily	Subjective symptom score (0–3) BTS Data collection point: week 4	Compared with placebo, there was no significant benefit in the FP group
Small et al[1599]	2008	2	RCT	CRSwNP (N = 447) MF NS 200 μg twice daily (n = 224) Placebo (n = 223)	Subjective symptom score (0–3) Data collection points: daily for 6.5 weeks	Compared with placebo, the MF group demonstrated significantly greater improvement in subjective symptom score first on day 13 and remained significantly elevated throughout study duration
Stjärne et al[1600]	2006	2	RCT	CRSwNP (N = 298) MF NS 200 μg once daily (n = 153) Placebo (n = 145)	Subjective symptom score (0–3) BTS Data collection points: week 4, week 8, week 12, week 16	Compared with placebo, the MF group demonstrated significantly greater improvement in subjective symptom score and BTS at all time points
Stjärne et al[1601]	2006	2	RCT	CRSwNP (N = 310) MF NS 200 μg once daily AM and placebo in PM (n = 102) MF NS 200 μg twice daily (n = 102) Placebo AM and PM (n = 106)	Subjective symptom score (0–3) Data collection points: week 4, week 12	Compared with placebo, the MF 200 μg twice-daily dosing group demonstrated significantly greater improvement in smell at W4. No significant benefit with every day dosing
Aukema et al[1602]	2005	2	RCT	CRSwNP (N = 54) FP NS 400 μg once daily (n = 27) Placebo (n = 27)	VAS loss of smell (0–100) Data collection points: week 2, week 6, week 12	Compared with placebo, the FP group demonstrated significantly greater improvement in VAS at week 12 only

(Continues)

TABLE IX-4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Small et al[1603]	2005	2	RCT	CRSwNP (N = 354) MF NS 200 μg once daily (n = 115) MF NS 200 μg twice daily (n = 122) Placebo (n = 117)	Subjective symptom score (0–3) Data collection: week 4, week 12	Compared with placebo, both MF groups demonstrated significantly greater improvement in subjective symptom score at week 4 and week 12
Djikstra et al[1604]	2004	2	RCT	CRS (n = 162) Underwent ESS followed by: FP NS 400 μg twice daily × 1 year (n = 53) FP NS 800 μg twice daily × 1 year (n = 53) Placebo twice daily × 1 year (n = 56)	VAS (0–100)	Compared with preoperative values, there was significant improvement in VAS in all groups Compared with placebo, there was no significant benefit in either FP groups
Parikh et al[1605]	2001	2	RCT	CRS (N = 22) FP NS (n = 9) Placebo (13)	Subjective symptom score (0–3)	Compared with placebo, there was no significant benefit in subjective symptom score in the FP group
Janowski et al[1606]	2001	2	RCT (4 budesonide groups vs placebo for 8 weeks)	CRSwNP (N = 183) Budesonide NS 128 μg once daily AM + placebo PM × 8 weeks Budesonide NS 128 μg twice daily × 8 weeks Budesonide NS 256 μg once daily AM + placebo PM Placebo × 8 weeks	Subjective symptom score (0–4) Data collection: daily diary symptom cards	Compared with placebo, all budesonide treatment groups demonstrated significantly greater improvement in subjective symptom scores Effect on symptoms became apparent within 1 to 2 days
Keith et al[1607]	2000	2	RCT	CRSwNP (N = 104) Nasal FP drops 400 μg once daily (n = 52) Placebo (n = 52)	Subjective symptom score (0–3) UPSIT® BTS Data collection: week 12	Compared with placebo, FP drops did not demonstrate significant benefit in any of the olfactory outcome measures
Penttilä et al[1608]	2000	2	RCT	CRSwNP (N = 142) FP NS 400 μg twice daily (n = 47) FP NS 400 μg once daily (n = 47) Placebo (n = 47)	UPSIT® BTS Subjective symptom score (0–3) Data collection points: week 4, week 8, week 12	Compared with placebo, patients with twice-daily dosing demonstrated statistically significant improvement in UPSIT® at one time point (not specified when)

(Continues)

TABLE IX-4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
						Compared with placebo, no significant benefit was noted on BTS or subjective symptom score
Mott et al[1609]	1997	3	Cohort	CRS (both polyp and nonpolyp patients) Nasal flunisolide twice daily (n = 45)	Subjective symptom score (0–3) CCCRC olfactory test Data collection: between week 8 to week 26	Compared with baseline, significant improvement was noted
Mastalerz et al[1610]	1997	2	RCT	CRS (n = 15) (all with aspirin sensitivity; 9 with polyps) FP NS 200 μg once daily × 4 weeks Placebo once daily × 4 weeks	Subjective symptom score (0–3) Data collection points: week 1, week 2, week 3, week 4	Compared with placebo, the FP NS group demonstrated significantly greater improvement in subjective symptom score at week 2, week 3, week 4
Lildholdt et al[1611]	1995	2	RCT	CRSwNP (N = 126) Nasal budesonide powder 200 μg twice daily (n = 40) Nasal budesonide powder 400 μg twice daily (n = 46) Placebo (n = 42)	Subjective symptom score Data collection points: week 4	Compared with placebo, there was no significant benefit in budesonide groups on subjective symptom score
Topical corticosteroid: irrigation						
Huang et al[1612]	2019	2	RCT	CRSwNP and CRSsNP Budesonide nasal irrigation (n = 30) Saline irrigations (n = 30)	VAS (0–10)	Compared with baseline, both groups demonstrated significant improvement Compared with saline, the budesonide irrigation group did not demonstrate significantly greater improvement on VAS
Harvey et al[1613]	2018	2	RCT	CRSwNP and CRSsNP MF nasal irrigation 2 mg and placebo spray once daily (n = 21) Placebo irrigation and MF NS 2 mg once daily (n = 23)	VAS (0–100) Data collection points: month 12	Compared with placebo, there was no significant benefit in the mometasone group on olfactory VAS score at month 12

(Continues)

TABLE IX-4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Rawal et al[1614]	2015	2	RCT	CRSwNP (N = 50) Budesonide nasal irrigation 0.12 mg twice daily (n = 25) Saline irrigations twice daily (n = 25)	UPSIT® PEA threshold test Data collection points: week 1 to 2, week 3 to 8, and month 3 to 6	Compared with baseline, neither group demonstrated significant benefit on USPIT or PEA test at any time point
Topical corticosteroid: exhalation-driven delivery						
Sindwani et al[1615]	2019	2	RCT	CRSwNP (N = 323) FP EDS 327 μg twice daily × 24 weeks (n = 79) FP EDS 186 μg twice daily × 24 weeks (n = 80) FP EDS 93 μg twice daily × 24 weeks (n = 81) Placebo EDS × 24 weeks (n = 82)	Subjective symptom score (0–3) Data collection points: week 4, week 8, week 12, week 16	Compared with placebo, FP groups demonstrated significant greater benefit in olfactory subjective symptom score at majority of time points
Leopold et al[1616]	2019	2	RCT	CRSwNP (N = 323) FP EDS 327 μg twice daily × 24 weeks (n = 82) FP EDS 186 μg twice daily × 24 weeks (n = 80) FP EDS 93 μg twice daily × 24 weeks (n = 80) Placebo EDS × 24 weeks (n = 79)	Subjective symptom score (0–3) Data collection points: week 4, week 8, week 12, week 16, week 24	Compared with placebo, all FP EDS dosing groups demonstrated significantly greater benefit in subjective symptom score at all time points
Kobayashi et al[1617]	2018	2	RCT	CRSwNP (N = 23) Exhaled Hydrofluoroalkane-134a beclomethasone dipropionate via metered dose inhaler × 4 weeks Placebo (n = 12)	OSIT-J Data collection point: week 4	Compared with baseline, both groups demonstrated significant benefit Compared with placebo, the exhaled corticosteroid group did not demonstrate any significant benefit
Soteres et al[1618]	2017	2	RCT	CRSwNP (N = 323) FP EDS 327 μg twice daily × 24 weeks (n = 82) FP EDS 186 μg twice daily × 24 weeks (n = 80) FP EDS 93 μg twice daily × 24 weeks (n = 80) Placebo × 24 weeks (n = 79)	Subjective symptom score (0–3) Data collection points: week 4, week 8, week 12, week 16, week 24	Significant improvement compared with placebo at all time points and at all doses

(Continues)

TABLE IX-4 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Topical corticosteroid: sinus implant						
Kern et al[1619]	2018	2	RCT	CRSwNP (N = 300) Bilateral MF sinus implants + MF NS once daily (n = 201) Sham placebo procedure + MF NS once daily (n = 99)	Subjective symptom symptom (0–5) Data collection points: month 3	Compared with placebo, the MF sinus implant group demonstrated significantly greater improvement in subjective symptom score at month 3

BTS = Butanol Threshold Score; CCCRC = Connecticut Chemosensory Clinical Research Center; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; EDS = exhalation delivery system; FP = fluticasone propionate; LOE = level of evidence; MF = mometasone furoate; NS = nasal spray; OSIT-J = Japanese Odor Stick Identification Test; PEA = phenylethyl alcohol; VAS = visual analog scale; WTS =

Oral antibiotics for OD in patients with CRSwNP.

Aggregate grade of evidence: B (Level 2: four studies; Level 3: one study).

Benefit: No clear benefit in subjective or objective olfactory outcomes.

Harm: Relatively low but adverse events in the medication groups included GI 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 OD in patients with CRSwNP.

Dupilumab for OD in patients with CRSwNP

Aggregate grade of evidence: A (Level 2: three studies).

Benefit: Dupilumab improves subjective and objective measures of OD compared with 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 OD 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 OD related to severe CRSwNP.

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

Mepolizumab for OD in patients with CRSwNP

Aggregate grade of evidence: B (Level 1: one study; 2: two studies).

Benefit: Mepolizumab may or may not improve subjective olfactory symptom scores, depending on other contributing patient factors, but objective measures of olfaction may not improve.

Harm: Injection site reaction, eczema, flu-like symptoms, headache, and muscle spasms, among others.

Cost:

Direct: High monetary cost per injection.

Indirect: Relatively low if home injections.

Benefits-harm assessment: Preponderance of potential harm versus potential benefit—specifically for smell loss—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 eosinophilic granulomatosis with polyangiitis; dosage used for trial in CRSwNP is higher than available for standard therapy of asthma and eosinophilic granulomatosis with polyangiitis.

Policy level: Option for use in patients with OD related to severe CRSwNP, but other biologics with more robust olfactory outcomes may be a better choice for improvement in this specific symptom.

Intervention: May consider as an option for OD related to patients with severe CRSwNP who have not improved despite other medical and surgical treatment options as

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Van Zele et al[1586]	2010	2	RCT	CRSwNP (N = 47) Study arms Oral doxycycline × 20 days (n = 14) Oral placebo × 20 days (n = 19)	VAS (0–10) Data collection points: week 1, week 2, week 4, week 8, week 12	Compared with placebo, doxycycline did not demonstrate significantly greater improvement in VAS at any time point.
Haxel et al[1565]	2014	2	RCT	CRS (N = 58) Study arms Oral erythromycin 250 mg daily (n = 29) Oral placebo (n = 29)	SS-ID Data collection points: week 2, week 14, week 26	Compared with placebo, there was no significant benefit noted in the erythromycin group on SS at any time point
Varvyanskaya et al[1567]	2014	2	RCT	CRSwNP (N = 66) Following ESS: Study arms MF NS (n = 22) Oral clarithromycin 250 mg once daily × 12 weeks (n = 22) Oral clarithromycin 250 mg daily × 24 weeks (n = 22)	SS-ID Data collection points: week 6, week 12, week 24	Compared with baseline, all groups demonstrated significant improvement Compared with control (MF NS), the clarithromycin × 24 week group was significantly improved on SS at week 6 only All remaining time points showed no no significant benefit in the clarithromycin groups
Dabirmoghaddam et al[1568]	2013	3	Cohort	CRSwNP (N = 40) Study arm: Oral clarithromycin 500 mg twice daily for 8 weeks (n = 40)	VAS (0–10) Data collection point: week 8	Compared with baseline, significant improvement was noted
Videler[1569]	2011	2	RCT	CRSsNP (N = 29) and CRSwNP(n = 31) Oral azithromycin 500 mg once daily for 3 days, then weekly for 11 weeks (n = 30) Oral placebo (n = 30)	SS-ID VAS (0–10) Data collection points: week 6, week 12, week 14	Compared with placebo, there was no significant benefit noted in the azythromycin group on SS or VAS at any time point

CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; LOE = level of evidence; MF = mometasone furoate; RCT = randomized controlled trial; SS = Sniffin' Sticks; SS-ID = Sniffin' Sticks identification only; VAS = visual analog scale.

part of a shared decision-making process, but other biologics with more robust olfactory outcomes may be a better choice for improvement in this specific symptom.

Omalizumab for OD in patients with CRSwNP

Aggregate grade of evidence: B (Level 2: four studies).

Benefit: Omalizumab improves subjective and objective olfactory measures of OD compared with 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 whether home or in-office injections.

Benefits-harm assessment: Likely benefit over harm for OD in patients with CRSwNP not responsive to medical and surgical standard of care.

Value judgments: Benefits are lost if therapy is discontinued and costs are an important consideration. Consider for patients with CRSwNP with concomi-

TABLE IX.6 Evidence for CRSwNP-related olfactory loss management with dupilumab

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Bachert et al[1560]	2019	2	RCT	CRSwNP (N = 448) Dupilumab 300 mg every 2 weeks × 52 weeks (n = 150) Dupilumab 300 mg every 2 weeks × 24 weeks then every 4 weeks × 28 weeks (n = 145) Placebo (n = 133)	Subjective symptom score (0–3) UPSIT® Data collection points: week 52	Compared with placebo, the dupilumab arms demonstrated significant improvement in UPSIT® and subjective symptom score at week 52
Han et al[1561]	2019	2	RCT	CRSwNP (N = 276) Dupilumab 300 mg every 2 weeks × 24 weeks (n = 143) Placebo (n = 133)	Subjective symptom score (0–3) UPSIT® Data collection points: week 24	Compared with placebo, the dupilimab arm demonstrated significant improvement in UPSIT® and subjective symptom sore at week 24
Bachert et al[1562]	2016	2	RCT	CRSwNP (N = 60) Dupilumab 600 mg loading then 300 mg weekly for a total of 16 weeks + MF NS (n = 30) Placebo + MF NS (n = 30)	Subjective symptom score (0–3) UPSIT® Data collection point: week 16	Compared with placebo, the dupilumab arm demonstrated significant improvement in UPSIT® and subjective symptom score at week 16

CRSwNP = chronic rhinosinusitis with nasal polyps; LOE = level of evidence; MF = mometasone furoate; NS = nasal spray; RCT = randomized controlled trial; UPSIT® = University of Pennsylvania Smell Identification Test.

tant poorly controlled allergic asthma who have not improved despite other medical and surgical treatment options.

Policy level: Recommendation for use in patients with OD related to severe CRSwNP.

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

Antileukotriene therapy for OD in patients with CRSwNP

Aggregate grade of evidence: B (Level 2: three studies).

Benefit: No clear benefit on olfaction but data limited. Zileuton may have added benefit for subjective olfaction when used as an adjunct to intranasal corticosteroids in AERD.

Harm: Montelukast has been associated with rare neuropsychiatric events in postmarketing 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 antileukotriene used specifically for olfaction.

Aspirin desensitization for OD in patients with AERD

Aggregate grade of evidence: B (Level 1: one study; Level 2: three studies; Level 3: one study).

Benefit: In patients with AERD, aspirin desensitization appears to improve OD based on subjective measures.

TABLE IX-7 Evidence for CRSwNP-related olfactory loss management with mepolizumab

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Bachert et al[1564]	2017	2	RCT	CRSwNP (N = 105) Mepolizumab 750 mg IV every 4 weeks for 24 weeks + FP NS 100 μg once daily (n = 54) Placebo +FP NS 100 μg once daily (n = 51)	VAS (0–10) SS-ID Data collection point: VAS: week 1, week 2, week 5, week 9, week 13, week 17, week 21, week 25 SS-ID: week 25	Compared with placebo, the mepolizumab group did not demonstrate a significant benefit at week 25 Compared with placebo, the mepolizumab group demonstrated significantly greater improvement in VAS at week 9 and this was sustained until week 25
Gevaert et al[1620]	2011	2	RCT	CRSwNP (N = 30) Mepolizumab 750 mg IV × 2 doses only, 28 days apart (n = 20) Placebo (n = 10)	Subjective symptom score (0–3) Data collection point: week 1, week 4, week 8, week 12, week 24, week 36, week 48	Compared with placebo, the mepolizumab group demonstrated a greater improvement in subjective symptom score, but this was not significant Improvement was sustained until week 48
Han et al[1646]	2021	1	RCT	CRSwNP (N = 407) Mepolizumab 100 mg IV × 13 doses, 4 weeks apart (n = 206) Placebo (n = 201)	VAS UPSIT® SNOT-22 Endoscopic polyp score	Compared with placebo, the mepolizumab did not cause a clinically significant improvement in smelling ability, despite significantly improving multiple other clinical end points

CRSwNP = chronic rhinosinusitis with nasal polyps; FP = fluticasone propionate; LOE = level of evidence; NS = nasal spray; RCT = randomized controlled trial; SNOT-22 = 22-item Sino-Nasal Outcome Test; SS-ID = Sniffin' Sticks identification only; IV = intravenously; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

Limited objective data are available. Additional benefits include reduced need for future surgical intervention, less medication use, and fewer physician visits.

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

Cost:

Direct: Moderate monetary cost of desensitization procedure. Minimal monetary costs of daily aspirin 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 OD related to AERD.

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

Oral corticosteroids for OD in patients with CRSsNP

Aggregate Quality of Evidence: C (Level 4: two 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 GI upset, hyperglycemia, rare severe reactions, cataracts, increased risk of infection, transient adrenal suppression, insomnia, and

TABLE IX-8 Evidence for CRSwNP-related olfactory loss management with omalizumab

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Gevaert et al[1563]	2020	2	RCT	CRSwNP (N = 138) Study arms: Omalizumab 75 to 600 mg every 2 to 4 weeks dosing (n = 72) Placebo (n = 66)	Subjective symptom score (0–3) UPSIT® Data collection points: week 8, week 16, week 24	Compared with placebo, the omalizumab group demonstrated significantly greater improvement in subjective symptom score and UPSIT® at week 8 and this was sustained to week 24
Gevaert et al[1563]	2020	2	RCT	CRSwNP (N = 127) Study arms: Omalizumab 75 to 600 mg every 2 to 4 weeks dosing (n = 62) Placebo (n = 65)	Subjective symptom score UPSIT® Data collection points: week 8, week 16, week 24	Compared with placebo, the omalizumab group demonstrated significantly greater improvement in subjective symptom score and UPSIT® at week 8 and this was sustained to week 24
Gevaert et al[1621]	2013	2	RCT	CRSwNP (N = 24) Omalizumab standard dosing × 16 weeks (n = 16) Placebo (n = 8)	Subjective symptom score Data collection point: week16	Compared with baseline, the omalizumab group demonstrated significantly greater benefit in subjective symptom score at week 16
Pinto et al[1622]	2010	2	RCT	CRSwNP (N = 14) Omalizumab standard dosing x 6 months (n = 7) Placebo (n = 7)	Subjective symptom score (0–3) UPSIT® Data collection point: month 3, month 5, month 6	Compared with placebo, the omalizumab group did not demonstrate any significant benefit in regards to subjective symptom score

CRSwNP = chronic rhinosinusitis with nasal polyps; LOE = level of evidence; RCT = randomized controlled trial; UPSIT® = University of Pennsylvania Smell Identification Test.

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 because of 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 OD in patients with CRSsNP is an option and should be individualized as part of a shared decision-making approach. Longer-term use of oral steroids for OD in patients with CRSsNP has not been studied and carries increased risk of harm to the patient.

Intranasal topical corticosteroids for OD in patients with CRSsNP

Aggregate grade of evidence: A (Level 2: seven studies; Level 3: one study).

TABLE IX-9 Evidence for CRSwNP-related olfactory loss management with anti-leukotriene therapy

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Stryjewska-Makuch et al[1623]	2019	2	RCT	AERD (N = 33) Following surgery: study arms: MF NS 200 μg twice daily Montelukast 10 mg once daily MF NS 200 μg twice daily + montelukast 10 mg once daily	B-SIT Data collection point: month 12	Compared with baseline, there was no significant benefit in B-SIT There was no significant difference in B-SIT score at month 12
Van Gerven et al[1624]	2018	2	Randomized, postoperative open-label	CRSwNP (N = 72) Following surgery: study arms: MF NS 300 μg 3 times daily (n = 36) MF NS 300 μg 3 times daily + montelukast 10 mg once daily (n = 36)	BAST-24 VAS (0–4) Data collection point: month 3, month 6, month 12	Compared with baseline, there was significant improvement in BAST score for both groups at all time points Compared with baseline, the MF NS only arms demonstrated significant benefit in VAS No significant difference in VAS scores at month 12
Dahlén et al[1625]	1998	2	RCT, crossover	AERD (N = 40) Oral zileuton 600 mg 4 times daily + baseline standard therapy (n = 40) Placebo + baseline standard therapy (n = 40)	VAS (0–10) Data collection points: week 6	Compared with placebo, there was a significant improvement in zileuton group on VAS at week 6

AERD = aspirin-related respiratory disease; BAST-24 = Barcelona Smell Test-24; B-SIT = Brief Smell Identification Test; LOE = level of evidence; MF = mometasone furoate; NS = nasal spray; RCT = randomized controlled trial; VAS = visual analog scale.

Benefit: The data are mixed with many studies failing to show a difference and a few showing modest improvement in subjective olfaction. There are 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 are significantly less robust compared with in patients with CRSwNP.

Policy level: Option for the management of OD in patients with CRSsNP.

Intervention: Topical nasal corticosteroids are an option for OD in patients with CRSsNP before or after sinus surgery.

Macrolide antibiotics for OD in patients with CRSsNP

Aggregate grade of evidence: B (Level 2: five 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: GI 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-10 Evidence for CRSwNP-related olfactory loss management with aspirin desensitization therapy

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Larivee et al[1626]	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 with control
Swierczynska-Krepa et al[1627]	2014	2	RCT	AERD (N = 20) Aspirin desensitization followed by aspirin 624 mg (n = 12) Placebo (n = 8)	VAS (0–10) Data collection point: month 1, month 2, month 3, month 4, month 5, month 6	Compared with placebo, the aspirin desensitization group demonstrated significantly greater improvement in VAS at month 1 and month 6 only
Fruth et al[1628]	2013	2	RCT	AERD (N = 31) Following surgery: Study arms: Aspirin desensitization with 100 mg aspirin over 3 years (n = 18) Placebo (n = 11)	SSl-ID Data collection: year 3	Compared with placebo, no significant benefit in the aspirin desensitization group was noted on SS-ID at year 3
Lee[1629]	2007	2	RCT	AERD (N = 137) Following aspirin desensitization: Discontinuation group Aspirin 325 mg twice daily Aspirin 650 mg twice daily	Subjective symptom score (0–5) Data collection point: year 1	Compared with baseline, significant improvement in subjective symptom score in all groups There was no significant difference between groups
Cho[1630]	2014	4	Retrospective cohort	AERD (N = 30) Following surgery patients underwent desensitization 1 month postoperatively Maintenance dosing at either aspirin 650 mg once daily in the AM and 325 mg at bedtime Aspirin 325 mg twice daily	Subjective symptom score (0–5) Data collection point: month 1, month 6, month 12, month 18, month 24, month 30	Compared with baseline, subjective symptom score significant improvement at month 1 and was sustained at month 30

AERD = aspirin-related respiratory disease; ESS = endoscopic sinus surgery; LOE = level of evidence; RCT = randomized controlled trial; SS-ID = SS-ID = Sniffin' Sticks identification only; VAS = visual analog scale.

Topical antifungals for OD in patients with CRSsNP

Aggregate grade of evidence: A (Level 2: three studies).

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 OD related to CRSsNP.

Medical therapy for OD in patients with AR. Antihistamines for OD in patients with AR

Aggregate grade of evidence: B (Level 1: one study; Level 2: three studies; Level 3: two studies).

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Liu et al[1631]	2018	Case series, retrospective	4	Oral antibiotics, mean 19 days (n = 17) Oral methylprednisolone for 6 days OR prednisone for 20 days (n = 28) Both oral antibiotics and oral steroids (n = 55)	Loss of smell (yes or no)	Combination antibiotic and steroid demonstrated the best improvement in subjective loss of smell
Ikeda et al[1332]	1995	Case series	4	Oral prednisolone, starting dose between 40 mg and 60 mg for 10 to 14 days with a quick taper	T&T olfactometer	Significant improvement of olfactory detection and recognition

CRSsNP = chronic rhinosinusitis without nasal polyps; LOE = level of evidence; T&T = Toyoda and Takagi.

Benefit: There is limited evidence that antihistamines improve OF 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 OD related to AR.

Intervention: Antihistamines are an option for use in treatment of OD related to AR.

Intranasal topical corticosteroids for OD in patients with AR

Aggregate grade of evidence: B (Level 1: one study; Level 2: six studies; Level 3: two studies).

Benefit: Data are mixed with some studies demonstrating benefit of intranasal corticosteroids over placebo in subjective and objective measures of OF 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 OD related to AR.

Immunotherapy for OD in patients with AR

Aggregate grade of evidence: B (Level 1: one study; Level 2: one study; Level 3: four studies).

Benefit: Improvement in subjective measures of OD related to AR among most studies. Data are limited with regard to objective measures.

Harm: Rare risk of severe anaphylactic reaction, higher in asthmatics and those taking β-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 OD related to AR, particularly those unresponsive to more conservative medical management measures and deemed low risk.

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Zeng et al[1593]	2019	2	RCT	CRSwNP and CRSsNP (n = 187) FP NS 200 μg once daily Oral clarithromycin 250 mg once daily	VAS (0–10) Data collection points: month 1, month 3, month 6, and month 12	Compared with baseline, both groups demonstrated improvement in VAS but no significant difference between groups
Harvey et al[1613]	2018	2	Double-blind RCT	CRS with and without polyps post-ESS (N = 44) 12 months of follow-up MF NS nasal irrigation 2 mg (n = 21) MF NS 2 mg (n = 23)	VAS (0–100)	No significant different between spray and irrigation
Zeng et al[1633]	2011	2	RCT	CRSsNP (n = 43) MF NS 200 μg once daily × 12 weeks Oral clarithromycin 250-mg tablet once daily × 12 weeks Data collection point: week 4, week 8, week12	Subjective symptom score (0–3) Data collection points: week 4, week 8, week 12	Compared with baseline, only the mometasone group demonstrated significant improvement at week 4 only No significant improvement in the clarithromycin group
Hansen et al[1634]	2010	2	RCT	CRSsNP (N = 20) Bidirectional spray 12 week course of: FP NS 400 μg twice daily (n = 10) Placebo (n = 10)	Subjective symptom score (0–3) Data collection point: week 12	Compared with placebo, the FP group demonstrated significantly greater improvement in subjective symptom score at week 12
Lund et al[1635]	2004	2	RCT	CRS (n = 167) Budesonide NS 128 μg twice daily × 20 weeks Placebo × 20 weeks	Subjective symptom score (0–3) (AM and PM) Data collection: week 20	Compared with placebo, the budesonide group demonstrated significantly greater improvement in subjective symptom score in the AM only at week 20

(Continues)

TABLE IX-12 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Djikstra et al[1604]	2004	2	RCT	CRS (N = 162) FP NS 400 μg twice daily × 1 year (n = 53) FP NS 800 μg twice daily × 1 year (n = 53) Placebo twice daily × 1 year (n = 56)	VAS (0–100)	Compared with preoperative levels, there was significant improvement in VAS in all groups Compared with placebo, there was no significant benefit in either FP groups
Parikh et al[1605]	2001	2	RCT	CRS (N = 22) FP NS (n = 9) Placebo (n = 13)	Subjective symptom score (0–3)	Compared with placebo, there was no significant benefit in subjective symptom score in the FP group
Mott et al[1609]	1997	3	Cohort	CRS (both polyp and nonpolyp patients) Flunisolide nasal drops twice daily (n = 45)	Subjective symptom score (0–3) Objective CCCRC olfactory test Data collection: between week 8 and week 26	Compared with baseline, there was significant improvement in subjective symptom and objective test scores.

CCCRC = Connecticut Chemosensory Clinical Research Center; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; FP = fluticasone propionate; LOE = level of evidence; MF = mometasone furoate; NS = nasal spray; RCT = randomized controlled trial; VAS = visual analog scale.

2 | Surgical treatment for CRS or AR-related olfactory loss

Surgical treatment of OD related to CRS and AR is primarily designed to improve the nasal airway, such that odorant-containing air can reach the OC. Additionally, surgery might allow for more effective delivery of topical medications that reduce mucosal inflammation.[1630] Most of the available surgical literature focuses on olfactory outcomes following endoscopic sinus surgery (ESS) in CRS. Although there are various surgical therapies for management of allergic nasal symptoms refractory to medical management, the available postsurgical olfactory outcomes data exist primarily for inferior turbinate surgery.[1631–1635]

In patients with CRS, OD is associated with the presence of polyps, asthma, DM, and older age.[1636] ESS is usually considered after appropriate medical therapy has failed to control bothersome symptoms.[1637] In most CRS studies investigating olfaction following ESS, patients are also treated with maintenance medical therapy (eg, intranasal corticosteroid). Therefore, it is important to remember that recommendations for surgery assume ongoing medical therapy in most instances. The available clinical studies assess OF through subjective measures (eg, VAS and subjective symptom scores) and objective psychophysical tests that include parameters such as forced-choice identification, smell discrimination, and olfactory thresholds.

There are few RCTs investigating olfactory outcomes following surgical intervention in CRS/AR. Much of the available olfactory literature is composed of prospective cohort studies or retrospective case series that focus on OF following ESS. Recent meta-analyses found that sinus surgery improves nearly all subjective and objective measures of olfaction in patients with CRS.[1638,1639] This benefit was most notable in patients with nasal polyposis and preoperative OD. While further high-level studies are needed, ESS may be recommended in patients with OD related to CRS in whom medical management has failed (Tables IX-19-IX-41 and Figure IX).

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Deng et al[1636]	2018	2	RCT	CRSsNP (n = 32), CRSwNP (n = 42) 3 months Oral clarithromycin 0.25 g/day and budesonide NS 256 μg once daily Budesonide NS 256 μg once daily	VAS (0–10)	Compared with baseline, there was significant improvement in both groups No difference between treatment groups
Haxel et al[1566]	2014	2	RCT	CRS Oral erythromycin 250 mg daily (n = 29) Placebo (n = 29) Total (N = 58) 3 months	SS-ID (12 odors)	Compared with placebo, there was no significantly greater improvement in the erythromycin group
Videler et al[1569]	2011	2	RCT	CRSsNP (n = 29) and CRSwNP(n = 31) Medical group (n = 30): oral azithromycin 500 mg once daily × 3 days, then weekly for 11 weeks Placebo (n = 30)11 weeks	SS-ID (12 odors) VAS (0-3)	Compared with placebo, there was no significantly greater improvement in the azithromycin group
Zeng et al[1633]	2011	2	RCT	CRSsNP (n = 43) MF NS 200 μg once daily × 12 weeks Oral clarithromycin 250 mg tablet once daily × 12 weeks Data collection point: week 4, week 8, week12	Subjective symptom score (0–3)	Compared with baseline, the mometasone group demonstrated significant improvement at week 4 only There was no significant improvement in the clarithromycin group
Wallwork[1637]	2006	2	RCT	CRSsNP without ESS Oral roxithromycin 150 mg once daily (n = 29) Placebo (n = 35)	SS-TDI	Compared with baseline, neither group demonstrated significant improvement There was no difference between roxithromycin and placebo

CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; LOE =level of evidence; MF = mometasone furoate; NS = nasal spray; RCT = randomized controlled trial; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; VAS = visual analog scale.

The available evidence on OF following inferior turbinate surgery in AR is very limited and is composed of prospective cohort studies and retrospective case series. Additionally, many of the included studies look broadly at patients with CRS, but the majority of these CRS cohorts include patients with AR. While these studies demonstrate improvement in subjective measures of olfaction following turbinate reduction, the data on objective measures are mixed.[1631,1633] Although turbinate reduction is generally performed in patients with AR who have nasal congestion refractory to medical therapy, no recommendation can be made for patients with AR-related OD because of the paucity of available evidence.

ESS is effective 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 patients with CRSwNP and those with poor preoperative

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Ebbens et al[1643]	2006	2	RCT	Nasal amphotericin B 10 mg (n = 59) Yellow-colored placebo (n = 57)	VAS (0–100)	Compared with placebo, there was no significant benefit in the topical antifungal group
Wechta et al[1644]	2004	2	RCT	Nasal amphotericin B 4 mg (n = 40) Placebo (n = 40)	VAS (0–10)	Compared with placebo, there was no significant benefit of the topical antifungal
Jiang et al[1645]	2018	2	RCT	Nasal amphotericin B 20 mg (n = 37) Placebo (n = 36)	UPSIT®	Compared with placebo, there was no significant benefit of the topical antifungal

CRSsNP = chronic rhinosinusitis without nasal polyps; LOE = level of evidence; RCT = randomized controlled trial; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

OF.[1639] Evidence for surgical management of OD related to AR is extremely limited and further investigation is warranted (Table IX-19).

ESS for OD in patients with CRS.

Aggregate grade of evidence: C (Level 2: five studies; Level 3: 30 studies; Level 4: five studies).

Benefit: ESS appears to improve subjective and objective measures of olfaction in patients with CRS. This benefit is most notable in patients with CRSwNP and those with severe baseline OD.

Harm: Risks of ESS are considered low but include bleeding, orbital injury, CSF leak, and risks of general anesthesia.

Cost:

Direct: Moderate to high upfront monetary costs associated with sinus surgery and postoperative care.

Indirect: Time required for procedure and recovery.

Benefits-harm assessment: Benefit over harm, particularly in patients with CRSwNP. Benefit to harm ratio less clear in patients with CRSsNP and those with minimal baseline OD.

Value judgments: Candidates with worse baseline OD and those with CRSwNP are more likely to benefit from ESS.

Policy level: Recommendation.

Intervention: As part of a shared decision-making process with the patient, it is reasonable to recommend ESS in those with OD related to CRS in whom medical management has failed.

Turbinate surgery for OD in patients with AR

Aggregate grade of evidence: C (Level 3: four studies; Level 4: one study).

Benefit: Five small studies that note improvement in subjective measures of olfaction in patients with AR. Two studies with objective data with mixed results. Overall, data are 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 because of 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 patients with AR who complain of nasal congestion despite medical therapy. No recommendation can be made for patients with AR whose chief complaint is OD.

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 OD related to intracranial disease, neurochemistry/neurotransmitter imbalances, and neurodegenerative disease is primarily designed to improve

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Klimek et al[1570]	2017	3	Prospective multicenter observational	AR (persistent) (n = 47) MP-AZE/FP NS twice daily for 3 months	SS-TDI	Compared with baseline, there was significant improvement in OF
Stuck et al[1555]	2015	1	Systematic review	AR 3 RCTs and 1 cohort study	Symptom scores BAST-24 VAS	There is limited evidence that antihistamines improve OF
Guilemany et al[1638]	2012	2	RCT	AR (n = 27) Oral levocetirizine (5 mg every day) Placebo	BAST-24 VAS	Compared with placebo, the levocetirizine group demonstrated significantly greater improvement in VAS only after 7 days
Kalpaklioglu et al[1639]	2010	2	RCT	AR (n = 62) AZE NS Triamcinolone NS	Subjective symptom score (0–3)	Compared with baseline, there was no significant improvement in either group No significant difference between the 2 treatment arms
Wober et al[1640]	1997	4	Cohort	AR (n = 211 children) AZE NS	Subjective symptom score (0–3)	Compared with baseline, there was a significant increase in the number of symptom-free patients (smell loss)
Gambardella et al[1641]	1993	2	RCT	AR (n = 30) Oral loratadine Placebo	Subjective symptom score (0–3)	No difference between the 2 treatment arms

AR = allergic rhinitis; AZE = azelastine hydrochloride; BAST-24 = Barcelona Smell Test-24; FP = fluticasone propionate; LOE = level of evidence; NS = nasal spray; OF = olfactory function; RCT = randomized controlled trial; SS = Sniffin' Sticks; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; VAS = visual analog scale.

the central processing of odor-evoked neural activity. This activity arrives in the OB from primary olfactory sensor neurons, where it is processed locally and then distributed to five distinct cortical areas for further processing: piriform cortex, olfactory tubercle, entorhinal cortex, amygdala, and anterior olfactory nucleus.[1677] The available clinical studies assess OF through subjective measures (eg, VAS or subjective symptom scores) and objective psychophysical tests that include parameters such as forced-choice identification, smell discrimination, and olfactory thresholds.[1678]

OD related to intracranial disease 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.[1679] Both transcranial approaches or endoscopic endonasal approaches have been associated with subsequent OD.[1679] In most studies, investigating olfaction following transcranial or endoscopic endonasal surgery, patients were treated with maintenance medical therapy (eg, intranasal corticosteroid). Recommendations for surgery to treat intracranial disease assume a risk of OD, and therapies for OD in this setting require further investigation.

There are limited controlled trials investigating medical therapy for OD from intracranial disease, neurochemistry/neurotransmitter, or neurodegenerative disease.[1678] Only post hoc cohorts were noted to improve in patients

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Klimeck et al[1570]	2017	3	Prospective multicenter observational	Mixed AR (n = 47) MP-AZE/FP NS twice daily for 3 months	SS-TDI	Compared with baseline, there was significant improvement in OF
Dalgic et al[1571]	2017	2	RCT	Seasonal AR (n = 30) Montelukast and MF NS (n = 10) Montelukast (n = 10) MF NS (n = 10)	SS-TDI	Compared with baseline, group 1 and 3 (those with MF) demonstrated significant improvement in SS-TDI No significant improvement in SS-TDI in the montelukast group alone
Stuck et al[1555]	2015	1	Systematic review	Mixed AR 5 RCTs and 1 cohort study	UPSIT® VAS Symptom score CCCRC olfactory test Chemosensory specific QOL SS-TDI	Limited evidence that topical steroids improve sense of smell
Higaki et al[1642]	2012	2	RCT	Seasonal AR MF NS Placebo	Questionnaire	Compared with placebo, mometasone NS did not demonstrate significant benefit
Kalpaklioglu et al[1639]	2010	2	RCT	Mixed AR (n = 70) AZE NS Tramcinolone NS	Symptom score	Compared with baseline, there was no significant improvement in either group No significant difference between the 2 treatment arms
Sivam et al[1572]	2010	2	RCT	Mixed AR (n = 17) MF NS Placebo	Chemosensory-specific QOL score UPSIT®	Compared with baseline, the mometasone group demonstrated significant improvement in chemosensory-specific QOL but not UPSIT®
Stuck et al[1573]	2003	2	RCT	Seasonal AR (n = 24) MF NS Placebo	SS-TDI	Compared with placebo, the mometasone group demonstrated significantly greater improvement on SS test (butanol)

(Continues)

TABLE IX-16 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Meltzer et al[1574]	1998	2	RCT	Mixed AR (n = 121) MF NS Placebo	CCCRC olfactor test	Compared with placebo, Mometasone group demonstrated significantly greater improvement in identification on CCRC
Golding-wood et al[1575]	1996	4	Case series	Mixed AR (n = 25) Beclomethasone nasal drops	UPSIT® VAS	Compared with baseline, the beclomethasone drops demonstrated significant improvement in subgroup in patients with initial subjective olfactory impairment

AR = allergic rhinitis; AZE = azelastine hydrochloride; CCCRC = Connecticut Chemosensory Clinical Research Center; FP = fluticasone propionate; LOE = level of evidence; MF = mometasone furoate; NS = nasal spray; OF = olfactory function; QOL = quality of life; RCT = randomized controlled trial; SS = Sniffin' Sticks; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

with posttraumatic anosmia (oral steroid pulse over 15 days) 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.[1680] 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.[1681]

The available evidence on OT is limited to neurodegenerative disease and is composed 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.[1678] One study of patients with PD tested OT of the test odors versus no training with same day and 1- to 2-month follow-up. Significant improvement was noted in odor identification in the trained group versus nontrained PD group at both the same day and 1- to 2-month follow-up.[1682] Performance on other odor tasks or identification of nontrained odors were not assessed. A recent meta-analysis of smell training found no significant improvement in smell function caused by PD, although there was a trend towards improvement in odor discrimination.[1683] Smell training improved OF, which is associated with structural changes in the olfactory processing regions of the brain, in healthy individuals.[1684] While further high-level studies are needed, smell training may be recommended in a patient with OD related to intracranial disease, neurochemistry/neurotransmitter, and neurodegenerative disease. Much of the available olfactory literature includes prospective cohort studies or retrospective case series that focus on OF as a diagnostic for neurodegenerative disease.

Evidence for smell training and medical treatment for smell dysfunction in intracranial, neurochemistry/neurotransmitter, and patients with neurodegenerative diseases 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.

Smell training therapy for OD in intracranial, neurotransmitter, and neurodegenerative disease

Aggregate grade of evidence: C (Level 3: two studies).

Benefit: Smell training may improve subjective and objective measures of olfaction in patients with neurodegenerative disease–caused 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 patients with PD.

Value judgments: As part of a shared decision-making process with patients, it is reasonable to recommend smell

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Stuck et al[1555]	2015	1	Systematic review	Mixed AR 1 RCT and 4 cohort studies	Subjective symptom score SS-TDI	Limited evidence that immunotherapy improves sense of smell
Tansuker et al[1576]	2014	4	Case series	Mixed AR (n = 12) SCIT	SS-TDI	Compared with baseline there was significant improvement on SS
Mun et al[1577]	2013	4	Case series	Mixed AR (n = 153) SLIT	Subjective symptom score	Compared with baseline, there was significant improvement in subjective symptom score
Kataotomichelakis et al[1578]	2013	4	Case series	Mixed AR (n = 36)	SS-TDI	Compared with baseline, there was significant improvement in subjective symptom score
Chang et al[1579]	2009	4	Case series	Mixed AR (n = 142) SLIT	Subjective symptom score	Compared with baseline, there was significant improvement in subjective symptom score
Radcliff et al[1580]	1996	2	RCT	AR (n = 36) SCIT Placebo	Subjective symptom score	Superior to placebo

AR = allergic rhinosinusitis; LOE = level of evidnce; RCT = randomized controlled trial; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SS = Sniffin' Sticks; SS-TDI = SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination.

training in patients with OD related to neurodegenerative diseases.

Policy level: Option.

Intervention: Consider smell training in patients with OD related to neurodegenerative disease given very low risk.

Medical therapy for OD in intracranial disease–, neurochemistry/neurotransmitter imbalance–, and neurodegenerative disease–related disease

Aggregate grade of evidence: C (Level 2: one study; Level 3: one study; Level 4: two 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 patients with PD with an aerobic exercise program. Overall, data are limited.

Harm: Olanzapine carries a black box warning of increased risk of stroke and death in elderly patients.

Cost:

Direct: Moderate monetary cost that varies based on 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 postiatrogenic anosmia, PD, olfactory reference syndrome, or dysosmias given a lack of clear benefit and risks associated with prescription medicine. Aerobic stationary bicycle exercise can be recommended to patients with PD for many reasons and may slow the decline of smell loss.

E | Treatment of other underlying systemic disease states

One of the less discussed areas of OD is the management of OD because of underlying systemic diseases. In

TABLE IX-18 Evidence for CRS-related olfactory loss management with ESS

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Zhao et al[1655]	2020	2	Meta-analysis	35 studies including 3164 patients with CRS were eligible for the meta-analysis	SS-TDI UPSIT® VAS QOD-NS B-SIT	ESS appears to be beneficial for improvement of OF in patients with CRSwNP Benefit is less clear in CRSsNP Further thorough and comprehensive studies need to be conducted
Moreno-luna R et al[1657]	2019	3	Prospective cohort	CRSwNP ESS with mucoplasty (free mucosal graft to ethmoid) (n = 10)	VAS	No significant improvement in olfaction
Zhang et al[1658]	2019	4	Retrospective	CRSwNP (N = 40) Eosinophilic polyps (n = 21) Noneosinophilic polyps (n = 19)	SS-TDI	Significant improvement in SS was noted 50% of patients improved by MCID (5.5)
Li et al[1659]	2018	4	Retrospective study	CRSwNP (n = 26)	VAS	Improvement in VAS was noted
Mattos et al[1660]	2018	3	Observational, multicenter cohort	CRS (n = 128)	QOD-NS	Significant improvement in QOD-NS noted MCID of 5.2 Majority of patients reporting abnormal baseline QOD-NS achieved an MCID
Walliczek-Dworschak et al[1661]	2018	3	Prospective cohort	CRSwNP (n = 21	SS-TDI STS	Significant improvement in SS but not STS
Haxel et al[1662]	2017	3	Prospective cohort	CRS (n = 41)	SS-ID (16 odors)	Significant improvement in SS
Kohli et al[1656]	2016	2	Meta-analysis	Mixed CRS patients	VAS SNOT-22 UPSIT® SS-TDI B-SIT	ESS improves nearly all subjective and objective measures of olfaction in patients with CRS patients Patients with nasal polyposis or preoperative OD improve to a greater degree
Andrews et al[1663a]	2016	3	Prospective cohort	CRSwNP (n = 60) CRSsNP (n = 53)	UPSIT® VAS	Significant improvement in UPSIT® and VAS
Chen et al[1665]	2016	3	Prospective, single institute cohort	CRSwNP (n = 42)	VAS	Significant improvement in VAS
Lind et al[1666]	2016	3	Prospective cohort	CRSwNP (n = 75) CRSsNP (n = 22)	SS-ID (12 odors)	Significant improvement in SS

(Continues)

TABLE IX-18 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Levy et al[1667]	2016	3	Prospective, multi-institutional cohort	CRS (n = 122)	B-SIT	Significant improvement in B-SIT Greater in CRSwNP
Soler et al[1668]	2015	3	Prospective cohort	CRS (n = 121)	QOD-NS	Significant improvement in QOD-NS Greatest improvement in patients with worse CT scores at baseline
Nguyen et al[1669]	2015	3	Prospective	CRSwNP (n = 65)	VAS	Significant improvement in VAS
Nguyen et al[1670]	2015	3	Prospective	CRSwNP (n = 69)	SS-TDI	Improvement in OF
DeConde et al[1671]	2015	3	Prospective	CRS (n = 311)	B-SIT	No significant improvement on B-SIT
Kim et al[1672]	2015	4	Cohort	CRS (n = 68)	VAS	No significant improvement on VAS
Kuperan et al[1673]	2015	3	Randomized prospective single-blinded	CRSwNP (n = 17)	VAS UPSIT®	OC surgery improves olfaction on UPSIT®
Hajjij et al[1674]	2015	4	Nested case-control	CRS (n = 40)	B-SIT	No significant improvement in B-SIT
DeConde et al[1675]	2014	3	Prospective cohort	CRS (N = 280) ESS (n = 222) Medical management (n = 58)	B-SIT	Compared with baseline, both groups improved No significant difference between groups
Jiang et al[1676]	2014	4	Case-control	CRSwNP (n = 52) CRSsNP (n = 48)	UPSIT®	No significant improvement in UPSIT®
Katotomichelakis et al[1677]	2014	3	Prospective	CRS (n = 116)	SS-TDI QOD-NS	Significant improvement in SS and QOD
Minwegen et al[1678]	2014	3	Prospective	CRS (n = 38)	SS-ID (12 odor)	Significant improvement in SS
Baradaranfar et al[1679]	2014	3	Nonrandomized clinical	CRS (n = 60) ESS followed by fluticasone Fluticasone	Subjective symptom score (0–10)	Compared with fluticasone alone, the ESS + fluticasone group showed significant improvement
Murthy et al[1680]	2013	3	Prospective observational	CRS (n = 71)	VAS	Significant improvement in VAS
Saedi et al[1681]	2013	3	Prospective	CRS (n = 89)	UPSIT®	Significant improvement in UPSIT®

(Continues)

TABLE IX-18 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Schriever et al[1682]	2013	3	Prospective	CRS (n = 113)	SS-ID (16 odors)	Significant improvement on SS-ID
Hsu et al[1683]	2013	3	Cohort	CRS (n = 29)	UPSIT®	≈50% of patient demonstrated improvement in OF
Saafan et al[1684]	2013	2	Prospective RCT	CRSwNP (n = 17)	VAS	Significant improvement on VAS
Bhandarkar et al[1685]	2011	3	Observational, prospective cohort	CRS (n = 142)	UPSIT®	Significant improvement on UPSIT® for patients with osteitis
Soler et al[1686]	2010	3	Prospective	CRS (n = 101)	UPSIT®	54.7% reported olfactory improvement of at least 4 points
Katotomichelakis[1687]	2010	3	Prospective	CRSwNP (n = 116)	SS-TDI	Significant improvement on SS
Konstantinidis et al[1688]	2010	3	Prospective	CRSwNP (n = 27)	SS-TDI	Improvement in SS in 74% of patients
Litvack et al[1689]	2009	3	Prospective, multi-institutional cohort	CRS (n = 111)	UPSIT®	Significant improvement in anosmics
Salama et al[1690]	2009	3	Prospective cohort	CRS (n = 143)	VAS	Significant improvement on VAS
Bugten et al[1691]	2008	3	Prospective controlled	CRSwNP (n = 57) CRSsNP (n = 45)	VAS	Compared with baseline, there was significant improvement on VAS in both groups No difference in degree of improvement between groups
Konstantinidis et al[1692]	2007	3	Prospective	CRSwNP (n = 18)	VAS SS	Significant improvement in SS and VAS
Lee et al[1693]	2007	3	Prospective	CRSwNP (n = 60)	VAS	Significant improvement in pediatric and adult groups No significant improvement in geriatric population
Alobid et al[1694]	2005	2	RCT	CRSwNP (n = 109) ESS followed by 12 months of intranasal budesonide Prednisone × 2 weeks followed by 12 months of intranasal budesonide	Subjective symptom score (0-3)	Compared with the prednisone group, the ESS group demonstrated significant improvement in symptom score at 6 months No difference at 12 months

(Continues)

TABLE IX-18 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Blomqvist et al[1559b]	2001	2	RCT	CRSwNP (n = 32) with symmetrical nasal airways where each side was randomly assigned to ESS vs no ESS followed by local nasal budesonide All patients received pretreatment with oral prednisolone for 10 days and topical budesonide for 1 month	BTT VAS	Compared with baseline, both sides improved Compared with medical treatment side, there was no additional benefit noted with surgery

B-SIT = Brief Smell Identification Test; BTT = Butanol Threshold Test; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; ESS = endoscopic sinus surgery; LOE = level of evidence; MCID = minimum clinically important difference; OD = olfactory dysfunction; OF = olfactory function; QOD-NS = Questionnaire of Olfactory Disorders-Negative Statements; RCT = randomized controlled trial; SNOT-22 = 22-item Sino-Nasal Outcome Test; SS = Sniffin' Sticks; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; STS = standardized test statistic; UPSIT® = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

this area, three main systemic causes emerge: hormonal diseases, autoimmune diseases, and vitamin and mineral deficiencies.

Treatment of OD related to endocrine and metabolic diseases

Diabetes mellitus (DM) is the most common cause of OD among patients with hormonal diseases.[1695] Several mechanistic hypotheses have been suggested, including elevated hemoglobin A_{1c} levels, microvascular and macrovascular complications, and polyneuropathies.[1695,1696] A strong association between OD and increased risk of cognitive impairment has been reported in type 2 DM.[1697,1698] In general, studies have revealed that type 2 DM with complications is associated with OD, while uncomplicated type 1 DM is not.[1699,1700] Therefore, prevention of diabetic complications plays an important role in the treatment of OD in these patients. Interestingly, hyperbaric oxygen therapy used in the adjuvant treatment of diabetic neuropathy significantly increased OF scores.[1701]

Thyroid diseases are also important causes of OD among patients with endocrine diseases, most commonly hyposmia in hypothyroidism.[1702] It is thought that the main reason for the development of hyposmia in hypothyroid patients is the role of thyroid hormone in OR maturation.[1703] Thyroid hormone replacement provides significant olfactory improvement in patients with frank hypothyroidism, as well as subclinical hypothyroidism.[1704,1705]

Obesity has recently become associated with metabolic OD and studies have shown that a loss of odor sensitivity is associated with an increase in body weight.[1706] 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.[1707] In a later similar study, weight loss surgery was able to return olfaction, and taste recovered to normal levels 6 months postprocedure.[1708]

Treatment of OD related to autoimmune diseases

Autoimmune diseases have long been associated with smell loss.[1709,1710] Specifically, patients with Sjögren syndrome and SLE have been found to commonly exhibit olfactory deficits. Schonfeld et al[1711] reported that the odor threshold and odor discrimination scores decreased in patients with SLE, and that OD correlated with disease severity and CNS involvement. SLE is a chronic autoimmune disease that requires long-term immunosuppressive therapy and causes neurocognitive damage caused by both the disease and the side effects of the treatments. Bombin et al[1712] 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. Another important cause of olfactory disorders among autoimmune diseases is IgG4-related disease, which has been associated with type 1 autoimmune pancreatitis, chronic sialoadenitis, kidney disease, periaortitis, and dacryoadenitis.[1713] Yagi-Nakanishi et al[1714] found that 52% of these patients had OD. Likewise, OD was found in patients with Mikulicz disease restricted to the salivary glands, which is also thought to be an IgG4-related disease

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

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Hamerschmidt et al[1651]	2016	3	Prospective cohort	CRS (AR and non-AR) (n = 57) Inferior turbinoplasty	Degree of smell improvement questionnaire	Majority of patients experienced "total improvement"
Assanasen et al[1650]	2014	3	Prospective cohort	CRS (AR and non-AR) (n = 48) Radiofrequency inferior turbinate reduction	VAS PEA test	Significant improvement in VAS but not T-PEA
Garzaro et al[1648]	2011	4	Case series	CRS (AR and non-AR) (n = 40) RITR	SS-TDI	Significant improvement in SS
Parida et al[1652]	2011	3	Prospective cohort	Perennial AR refractory to medical management (n = 50) Radiofrequency volumetric tissue reduction	VAS	Significant improvement in VAS
Ikeda et al[1649]	2006	3	Prospective case series	AR (n = 56) Functional inferior turbinosurgery and resection of posterior nasal nerve	VAS	Improvement noted in anosmics

AR = allergic rhinosinusitis; CRS = CRS = chronic rhinosinusitis; LOE = level of evidence; PEA = phenylethyl alcohol; RITR = radiofrequency inferior turbinate reduction; SS = Sniffin' Sticks; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; VAS = visual analog scale.

TABLE IX-20 Evidence for smell training in intracranial disease–, neurochemistry/neurotransmitter imbalance–, and neurodegenerative disease–related olfactory loss management

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Haehner et al[1703]	2013	3	Prospective, controlled, nonblinded	Patients with PD underwent OT twice daily for 12 weeks with 4 odorants (n = 35) Controls (n = 35)	SS-TDI Threshold for 3 other trained odorants	The only significant difference was in total SS-TDI (mean increase 2.4) and discrimination scores 20% vs 9% met MCID Independent of age, sex, severity, and duration of disease
Knudsen et al[1700]	2015	3	Prospective, nonblinded, cohort	Patients with PD: smell retraining of odors on the test (n = 34) HCs: smell retraining (n = 26) Patients with PD: no training (n = 20) Training consisted of 1 session of two 10-minute exposures to the SS odors with visual and written cues	SS-ID Measured pretraining and immediately posttraining Retest in 8 after 4 to 8 weeks	Improvement in identification (increase of 2.2) was noted the same day Benefit persisted at retest

HC = healthy control; LOE = level of evidence; OT = olfactory training; PD = Parkinson disease; MCID = minimum clinically important difference; SS = Sniffin' Sticks; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination.

TABLE IX-21 Evidence for medical therapy for management of intracranial disease–, neurochemistry/neurotransmitter imbalance–, and neurodegenerative disease–realated olfactory loss

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Haehner et al[1705]	2013	2	Single-center, prospective, randomized, controlled, double-blind	Patients with a diagnosis of PD: rasagiline 1 mg once daily for 120 days (n = 17), placebo (n = 17)	SS-TDI Retronasal testing Olfactory ERP	No significant improvement for any component of TDI score, retronasal testing, or olfactory ERP
Haehner et al[1706]	2015	4	Single-center, cross-sectional	Patients with diagnosis of PD (n = 224): rasagiline 1 mg every day (n = 74), controls (n = 150)	SS-TDI	No significant difference for TDI score or any subcomponent Treated patients with disease <8 years had better discrimination
Albers et al[1698]	2018	4	Case report	ORS (n = 1)	POEM	Improvement in symptoms and odor identification after treatment with olanzapine
Rosenfeldt et al[1699]	2016	3	Single-site, unblinded, placebo-controlled	Patients diagnosed with PD: aerobic exercise (n = 23), placebo (n = 15)	UPSIT®	Stabilization of UPSIT® over 8 weeks of exercise relative to controls (3-point decline over 8 weeks)

ERP = event-related potential; LOE = level of evidence; ORS = olfactory reference syndrome; PD = Parkinson disease; POEM = Percepts of Odor Episodic Memory; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, and identification; UPSIT® = University of Pennsylvania Smell Identification Test.

and was found specifically in patients with increased IgG4 plasmacytes in the nasal mucosa.[1715] It has been demonstrated that steroids are very effective in the treatment of IgG4-related disease, helping to reverse associated epithelial damage as well as CNS dysfunction.[1714]

Treatment of OD related to mineral and vitamin deficiency

For many years, the questions of whether zinc deficiency can cause OD and whether zinc replacement can be a useful treatment option have been investigated.[1716] It is now known that zinc deficiency only rarely causes OD, but it is much more commonly associated with taste deficits that typically reverse with zinc replacement.[1717,23a] 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.[1718] This concept was adapted as a means of chemoprophylaxis against polio in the era before vaccination. Topical intranasal zinc, in high concentration, was applied to the OC 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.[1719] Although the majority of children recovered their sense of smell, there were anecdotal reports of permanent smell loss.[1720] More recently, over-the-counter topical intranasal zinc sprays were marketed to treat the common cold but later implicated in the development of anosmia based on two case series with some overlapping patients.[1721,1722] 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 OC was very limited with the spray, and the well-established cause of typical postviral anosmia was hard to exclude.[1723] 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 a beneficial effect on OF.[29a] In contrast, when no deficiency is noted, vitamin A, given systemically at a dosage of 10,000 IU/day for 3 months, was reported to be ineffective on reversing olfactory loss.[1724] Five years after this initial study,

TABLE IX-22 Section evidence summary: Treatment of other underlying endocrine diseases

Study	Year	LOE	Disease	Study design	Study groups	Clinical end point	Conclusions
Weinstock et al[1707]	1993	3	DM	Cohort	111 patients with DM	Odorant confusion matrix	Presence of macrovascular disease in patients with DM was found to be associated with OD
Brady et al[1708]	2013	2	DM	Double-blinded, placebo controlled-crossover	74 patients, 19 healthy with DM	SS-TDI	Presence of neuropathic pain in DM was found to be associated with OD
Sanke et al[1709]	2014	3	DM	Cohort	250 patients with DM	Olfactory and cognitive functions: Open Essence test MMSE	Olfactory essence test score of the probable dementia group with type 2 DM was significantly lower than other groups
Yulug et al[1710]	2020	2	DM	Double-blinded, placebo-controlled, crossover	46 patients, 16 prediabetic, 15 type 2 DM	Olfactory and cognitive functions SS-TDI MMSE	Olfactory and cognitive test scores different in DM and pre-DM groups There is a strong association between OD and specific memory impairment in a population with pre-DM and DM
Altundag et al[1711]	2017	2	Type 1 DM	Double-blinded, placebo controlled-crossover	70 patients, 31 HCs, 39 non-complicated type 1 DM	Olfactory and gustatory functions: SS-TDI Taste strips	Olfactory and gustatory functions scores did not decrease in noncomplicated type 1 DM
Gouveri et al[1710]	2014	2	Type 2 DM	Double-blinded, placebo controlled-crossover	154 patients, 119 type 2 DM	SS-TDI	Diabetic complications were associated with OD
Veyseller et al[1713]	2016	4	Type 2 DM	Cohort	62 patients, 30 HCs	CCCRC olfactory test	Diabetic neuropathy leads to diabethic olfactopathy Hyperbaric oxygen treatment can be used in diabetic olfactopathy
McConnell et al[1714]	1975	4	Hypothyroid	Case series	18 hypothyroid patients	Olfactory and taste functions (taste solutions, pyridine-nitrobenzene for OFs)	Untreated hypothyroidism leads to olfactory and gustatory dysfunction reversible with thyroid hormone replacement

(Continues)

TABLE IX-22 (Continued)

Study	Year	LOE	Disease	Study design	Study groups	Clinical end point	Conclusions
Günbey et al[1715]	2015	3	Hypothyroidism	Cohort	90 patients, 45 primary hypothyroid patients	SS-TDI	Free T3 levels were found to have a more significant relationship with olfactory parameters than thyroid-stimulating hormone or free T4 levels
Baskoy et al[1717]	2016	3	Hypothyroid months L-thyroxine treatmen	Cohort	59 patients, 28 subclinical hypothyroid patients	SS-TDI 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[1718]	2019	4	Obesity	Review	Review of 19 studies	Multiple measures Meta-analysis of SS-TDI performed on 9 studies	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[1719]	2012	3	Obesity	Cohort	95 patients, 55 gastric bypass surgery	B-SIT	Gastric bypass surgery does not appear to influence OF
Holinski et al[1720]	2015	4	Obesity	Case series	44 orbidly obese patients undergoing bariatric surgery	SS-TDI Taste strips	Both olfactory and gustatory functions improve 6 months after bariatric surgery

B-SIT = Brief Smell Identification Test; CCCRC = Connecticut Chemosensory Clinical Research Center; DM = diabetes mellitus; HC = healthy control; LOE = level of evidence; MMSE = Mini-Mental Status Examination; OD = olfactory dysfunction; OF = olfactory function; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination.

however, vitamin A applied intranasally as an add-on treatment in conjunction with OT, was suggested to be effective for the treatment of postinfectious olfactory loss, but it was an uncontrolled, unblinded, retrospective study, disallowing for any conclusion about true efficacy in a nondeficient patient population.[1725]

Iron deficiency is also associated with olfactory deficits[1726] that improve with iron replacement.[1727] Vitamin B12 deficiency is also a cause of reversible OD, 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 caused by PD. Håglin et al[37] Reported that thiamine and folic acid deficiency in the diet, especially 2 to 8 years before the diagnosis of PD, led to OD. It was suggested by Heilmann at al[38] that vitamin B1 deficiency causes odor loss and that long-term replacement can be an effective treatment. In this study, vitamin B treatment was compared with local and systemic corticosteroid treatments.

TABLE IX-23 Section evidence summary: Treatment of other underlying autoimmune diseases

Study	Year	LOE	Disease	Study design	Study groups	Clinical end point	Conclusions
Perricone et al[1721]	2013	4	Autoimmunity SLE	Review	Articles about autoimmunity and smell	Relationship between autoimmune diseases and OF	OR gene clusters close to major histocompatibility complex
Strous et al[1722]	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[1723]	2009	2b	SLE	Cohort	100 participants, 50 SLE	SS-TDI	OF decreased in patients with SLE
Bombini et al[1720]	2018	2b	SLE systemic sclerosis	Cohort and review	366 participants, 143 SLE patients	SS-TDI	OF decreased in patients with SLE and systemic syclerosis
Stone et al[1725]	2012	2b	IgG4-related disease	Cohort and review	Review	Mechanism of disease	Multiple immune-mediated mechanisms contribute to the inflammatory processes of IgG4-related disease
Yagi-Nakanishi et al[1726]	2016	4	IgG4-related disease	Case series	25 patients with IgG4-related disease	T&T olfactometer	OD is an important manifestation of IgG4-related disease and may be reversible
Takano et al[1727]	2011	4	Mikulicz disease (also an IgG4 disease)	Case series	44 patients with Mikulicz disease	T&T olfactometer	OD may be associated with infiltration of nasal mucosa by IgG4-positive plasmacytes in Mikulicz disease

LOE = level of evidence; OD = olfactory dysfunction; OF = olfactory function; OR = olfactory receptor; SLE = systemic lupus erythematosus; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi.

Patients with many causes of OD such as postinfectious, 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 1 month post-smell loss, with no control or placebo, no definitive conclusion can be made. While discussing the olfactory effects of B vitamins, thiamine, 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 OD, both directly and indirectly via secondary vitamin B deficiency.[39]

While examining the effects of vitamins and minerals on OF, their mutual interactions and metabolism should not be overlooked, and, in addition, various common mutations (such as methyltetrafolate reductase enzyme mutation) will cause differences in homocysteine metabolism and subsequent changes in vitamin B metabolism.[40]

TABLE IX-24 Section evidence summary: Treatment of underlying vitamin deficiency

Study	Year	LOE	Disease	Study design	Study groups	Clinical end point	Conclusions
Henkin et al[1728]	1975	4	Zinc deficiency caused by histidine administration to treat progressive systemic sclerosis	Case series	6 patients with progressive systemic sclerosis taking histidine amino acid: 4 female 2 male	Single olfactory and gustatory function tests (pyridine for smell, urea for taste)	Acute zinc loss caused by histidine treatment caused olfactory and gustatory dysfunction and treated rapidly with zinc administration
Jafek et al[1734]	2004	4	Anosmia after zinc gluconate	Case series	n = 10	Colorado CS questionaire	Zinc-induced anosmia occurs after exposure to OE
Alexander and Davidson[1735]	2006	4	Zinc-induced anosmia syndrome	Case series	(n = 17)	UPSIT®	Zinc-induced anosmia occurs after the exposure of zinc cation to OE
Garrett-Laster et al[1737a]	1984	4	Vitamin A–deficient patients (n = 27) treated with oral vitamin A (10,000 μg/day) for 4 weeks	Descriptive (noncontrolled)	37 Vitamin A deficient patients	Pyridine detection and recognition threshold improvement	Significant improvement in olfactory threshold
Reden et al[1738]	2012	2	Postinfectious, posttraumatic anosmia treatment with systemic vitamin A	Double-blind randomized, controlled clinical	52 patients (n = 26 placebo, n = 26 systemic vitamin A, 10,000 IU, 3 months)	SS-TDI	Systemic application of vitamin A not useful for treatment of postinfectious or posttraumatic olfactory loss
Hummel et al[1739]	2017	4	Postinfectious anosmia treatment with smell training and intranasal vitamin A	Retrospective cohort	170 patients (n = 46 smell training only, 124 smell training + intranasal vitamin A, 10,000 IU	SS-TDI	Intranasal vitamin A could potentially be useful for treatment of postinfectious olfactory loss but more robust data are needed

(Continues)

TABLE IX-24 (Continued)

Study	Year	LOE	Disease	Study design	Study groups	Clinical end point	Conclusions
Kopala et al[1740]	1995	3	AN	Cohort	77 participants (n = 27 patients with AN)	UPSIT®	UPSIT® scores normal for patients with AN Transient metabolic or nutritional disturbances are unlikely to be responsible for long-term OD
Dinc et al[1741]	2016	3	IDA	Cohort	100 participants (n = 50 IDA patients)	SS-TDI	OF decreases in IDA patients
Hansen et al[1742]	2017	4	IDA	Case series	3 patients with IDA	Olfactory craving symptoms (self-reporting)	IDA is cause of desideros-mia that is an olfactory craving phe-nomenon and this phe-nomenon is treated with IDA treatment: iron
Derin et al[1743]	2016	2	Vitamin B12 deficiency	Double-blind randomized, placebo-controlled clinical	73 patients (n = 39 patients with low level vitamin B12)	SS-TDI	OD may be present in patients with vitamin B12 deficiency
Håglin et al[1745]	2016	3	Vitamin B intake, PD	Cohort	420 participants (n = 84 cases, PD)	B-SIT	Low thiamin (vitamin B1) and folate in the diet 2 to 8 years prior in PD patients related with OD at the time of PD diagnosis
Heilmann et al[1746]	2004	3	Posttraumatic, postinfectious olfactory loss, vitamin B and corticosteroid treatment	Cohort	192 patients (n = 72 cases, postinfectious olfactory loss)	SS-TDI	Systemic vitamin B treatment is not effective after 2 months, but if vitamin B given for full 6 months,

(Continues)

TABLE IX-24 (Continued)

Study	Year	LOE	Disease	Study design	Study groups	Clinical end point	Conclusions
							treatment may be useful for smell function, although there was no control group and no time restriction controlling for spontaneous resolution
Selhub et al[1747]	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

AN = anorexia nervosa; IDA = iron deficiency anemia; LOE = level of evidence; OE = olfactory epithelium; OF =olfactory function; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

The treatment of OD secondary to endocrine, metabolic, autoimmune, and vitamin and mineral deficiency should be based on the treatment of the primary disorder.

Investigating the treatment of metabolic and endocrinologic diseases in patients to improve OD

Aggregate grade of evidence: C (Level 2: four studies; Level 3: five studies; Level 4: four studies).

Benefit: In patients with OD, evaluation for metabolic and endocrinologic diseases may potentially help diagnose the reason for OD. 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, DM, and obesity.

Value judgments: Endocrine and metabolic diseases can cause OD and correcting these can correct OD.

Policy level: Evaluating and treating patients with olfactory disorders and suspected or known DM, hypothyroidism, or obesity is recommended.

Intervention: Laboratory tests, including serum thyroid-stimulating hormone, glucose, and hemoglobin A_{1c} levels should be considered in individuals with OD and suspected hypothyroidism or DM, and referrals to specialists who can treat these underlying disorders should be made.

Investigating and treating autoimmune diseases in patients with related OD

Aggregate grade of evidence: C (Level 2b: three studies; Level 4: four studies).

Benefit: In patients with OD, evaluation for autoimmune diseases, especially Sjögren syndrome, 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 OD, 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.

F | If no underlying disease state to correct

1 | Treatment with corticosteroids

The evidence for steroids, both topical and systemic, as treatment for nonsinonasal disease–related olfactory loss is limited, as recently highlighted in a systematic review.[1727] While excluding rhinosinusitis and rhinitis, the causes of these olfactory losses remain heterogeneous and include postinfectious, posttraumatic, and idiopathic causes. Baseline severity of OD is varied among patients 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 nonsinonasal disease olfactory loss (Table IX-25). In three uncontrolled cohort studies (Level 4), 20% (23 of 117 patients) demonstrated clinically significant improvement in olfactory measures using topical steroid sprays.[1728–1730] However, a small RCT found no olfactory benefit from the addition of topical steroid sprays (fluticasone) in patients who were previously responsive to oral steroids.[1731] Currently, there are 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 nonsinonasal inflammatory-related olfactory loss. Individuals using twice-daily budesonide nasal rinses along with OT were more likely to achieve clinically significant improvement compared with saline rinses with OT (43.9% versus 26.9%, $P = 0.039$).[1732] Additional RCTs would be useful to corroborate this finding.

There is a paucity of studies evaluating the optimal head position for topical steroid delivery to the OC, with most utilizing cadaveric models (Table IX-26). Two studies reported successful irrigation delivery to the OE using the head-over-sink position.[1733,1734] Even in maximal postsurgical conditions (modified Lothrop), topical rinses had superior OC penetration compared with topical sprays.[1734] Other head positions (head-tilted forward, vertex-to-floor, neutral position, head reclined, and lateral head low) have demonstrated variable success in topical delivery.[1733–1741] Middle turbinate resection failed to improve delivery of irrigation to the olfactory mucosa.[1742] 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 nonsinonasal disease OD.

Meanwhile, the use of systemic steroids alone in nonsinonasal 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 to 60 mg/day and a 2-week taper. Five cohort studies with a total of 553 patients demonstrated that 16.4% to 49.6% of patients treated with systemic steroids had a significant improvement in olfaction threshold measurements[1728,1743–1746] with two studies demonstrating clinically meaningful improvements of TDI in 12% to 29% of patients.[1728,1746] Systemic steroids were not beneficial in a small retrospective case series of patients who were nonrespondent to topical therapy[1747] and an RCT of patients with PTOD, although this study may have been underpowered.[1748] Systemic steroids appear to have an additive benefit when used in conjunction with topical steroids.[1749] Three retrospective studies totaling 554 patients reported improved OF in patients receiving systemic and topical steroids compared with topical steroid sprays alone.[1750–1752] For most of these studies, inclusion of patients early (<6 months) 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, although the potential risks of systemic corticosteroids given even in short bursts have been well documented.[1753]

Overall, the literature supporting the use of steroids in nonsinonasal inflammatory causes of anosmia is limited with few RCTs. Topical steroid sprays are not recommended given their general lack of efficacy and limited delivery to the OC. Topical steroid rinses are recommended, with one high LOE 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 large-scale RCTs are required to further elucidate their efficacy, dosage, and timing in the treatment of nonsinonasal disease OD.

The use of steroids to treat OD is not related to underlying inflammatory sinonasal disease

Aggregate grade of evidence: C (Level 2: four studies; Level 3: one study; Level 4: 17 studies; Level 5: five studies).

Benefit: Use of budesonide irrigations and systemic steroids may improve anosmia secondary to nonsinonasal inflammatory causes of OD.

TABLE IX.25 Systematic review of topical steroid treatments for OD

Author	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Yan, et al.[1749]	2019	2	Systematic EBRR	Patients with olfactory loss treated with systemic steroids, topical steroids, or both	Studies included only objective psychophysical test confirmation of smell loss, eg, UPSIT® and SS-TDI	Topical steroid sprays are NOT effective in treating OD from nonsinonasal inflammatory etiologies, but topical steroid irrigations are effective in treating this patient population
Blomqvist et al[1753]	2003	2	Double-blind RCT	Population: 30 URI or idiopathic Severity of smell loss: mixed, details NA Duration of loss: up to 6.6 years Treatment: all patients pretreated with 10 days of oral prednisolone 40 mg twice daily taper + 10 days of fluticasone spray (only improved patients included) 20 patients: topical fluticasone spray: 2 twice daily (200 μg every day) × 6 months 10 patients: placebo spray 10 patients: no treatment	Follow-up: 6 months CCCRC olfactory test	No statistically significant difference in olfactory thresholds or scored sense of smell among the 3 groups No treatment group had a decrease in olfactory threshold at 2 months
Fleiner et al[1751]	2011	4	Prospective cohort	Population: 13 URI or idiopathic Severity of smell loss: mixed, details NA Duration of loss: 2 to 120 months (median 28 months) Treatment: ceclomethasone spray twice daily × 4 weeks	Follow-up: 4 weeks SS-TDI	Median improvement TDI score 2 points 2 of 13 patients (15.4%) had clinically relevant change in TDI score (6 points)
Fleiner et al[1752]	2012	4	Retrospective case series	Population: 31 URI, posttraumatic, idiopathic Severity of smell loss: 13 of 31 (42%) hyposmic, 18 of 31 (58%) anosmic Duration of loss: 10.5-36 months (median 21 months) 18 patients with OT only 13 patients treated with topical steroid (dose NA)	Follow-up: 8 months SS-TDI	Steroid + olfactory training mean TDI improved 6.83 points (P<0.001) vs olfactory training mean TDI improved 2.20 points 5 of 13 patients (38.4%) had clinically significant improvement (≥6 patients) at 8 months with topical steroids + OT

(Continues)

TABLE IX.25 (Continued)

Author	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Nguyen and Patel[1754]	2018	2	RCT	Population: 66 treated/67 controls All non-CRS or rhinitis causes, duration of loss: >6 months Severity of smell loss: NA Treatment Budesonide 0.5 mg/2 mL twice daily nasal rinses + OT Saline rinses + OT	Follow-up: 6 months UPSIT®	43.9% significant improvement in budesonide rinses + olfactory training vs 26.9% improvement in saline + olfactory training ($P = 0.039$) Younger age and shorter duration of olfactory loss were significant predictors of improvement ($P<0.0001$ for both)
Stenner et al[1750]	2008	4	Retrospective Case series	Population: 73 non-CRS causes Severity of smell loss: mixed, details NA Duration of loss: 2 to 520 months (mean 55 months) Treatment: All patients treated with beclomethasone 15 mg every day × 20-day taper After 12 weeks, patients treated with topical budesonide 1.5 mg twice daily or budesonide + neomycin 7.5 mg every day Follow-up: 12 weeks SS-TDI	Follow-up: 12 weeks SS-TDI	Oral steroids improved mean TDI from 15.5 to 18.7 ($P<0.001$) 27% had clinically meaningful improvement of TDI by at least 6 points Topical treatment did not further improve TDI overall (18.7 to 18.9 points), but 12% had clinically meaningful improvement in TDI No change with topical antibiotics

CCCRC = Connecticut Chemosensory Clinical Research Center; CRS = chronic rhinosinusitis; EBRR = evidence-based review with recommendation; LOE = level of evidence; NA = not available; OT = olfactory training; RCT = randomized controlled trial; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, identification; URI = upper respiratory infection.

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 the use of topical or systemic steroids for nonsinonasal disease–related anosmia. However, side effects of systemic steroids are well known and must be considered on a case-by-case basis.

Value judgments: Steroid irrigations and systemic steroids may help improve nonsinonasal 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.

2 | Olfactory training

OT is performed by smelling specific sets of odors twice daily for an extended period of time. Hummel et al,[1755] in a landmark study, first reported benefit from OT in

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	Conclusions
Lam et al[1755]	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 with sprays directed away from septum Irrigation: head-over-sink position	Irrigations delivered greater surface area and intensity of staining compared with sprays ($P<0.05$)
Beule et al[1756]	2013	5	Cadaveric	Population: 15 cadaveric heads s/p endoscopic modified Lothrop procedure and complete sphenoeth-moidectomy	Assessed NS and squeeze bottle (50 mL, 100 mL, and 200 mL) Head position: bending over the sink vs vertex to floor	Nasal irrigation 200 mL stained surface of olfactory region >100 mL, 50 mL, and spray Bending over the sink stained the OE better than vertex to the floor
Scheibe et al[1757]	2008	4	Observational	Population: 15 healthy volunteers	Assessed the distribution of topical pipette (head reclined as much as possible), NS, and system producing squirts	Squirt reached OC in 73% of participants ($P<0.001$)
Herranz Gonzalez-Botas and Seara[1758]	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 OC
Cannady et al[1759]	2005	4	Observational	Population: 6 patients post-FESS with a total of 11 sides	Compared delivery of spray in vertex to floor position for 1 and 5 minutes with atomizer in upright position	Vertex to floor position with 5 minutes had a significant increase of spray delivery to the OC ($P = 0.012$)
Rudman et al[1760]	2011	4	Observational	Population: 9 volunteers	Detected radiopaque contrast solution in spray vs drops Drops were instilled in the vertex-to-floor position	The OC was not penetrated by either spray or drops >50% of the time and there was no significant difference between the 2 methods ($P>0.05$)
Manes et al[1761]	2011	5	Cadaveric	Population: 5 cadavers	Investigated the distribution of aerosol delivered via powered nasal nebulizer in unoperated nose, post-FESS, and post-FESS 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 OC ($P = 0.885$)

(Continues)

TABLE IX.26 (Continued)

Author	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Raghavan and Logan[1762]	2000	5	Cadaveric	Observed distribution of nasal drops in cadaveric specimens in head back, head down and forward, lateral head low, and lying head back positions	NA	Head down and forward position demonstrated distribution of drops to OC
Mori et al[1763]	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 OC in 96% and 75% of decongested patients and patients without decongestion, respectively
Kidwai et al[1764]	2017	5	Cadaveric	Population: 4 cadaver heads	240-mL irrigation bottle in head over sink position in unoperated and postmiddle turbinate resection	No significant difference in the delivery of irrigation to the OC before and after middle turbinate resection ($P = 0.340$)

FESS = functional endoscopic sinus surgery; LOE = level of evidence; OC = olfactory cleft; OE = olfactory epithelium; NA = not available; NS = nasal spray.

patients with olfactory loss where patients smelled four 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 OT (COT), including smells from categories of floral (rose), fruity (lemon), resinous (eucalyptus), and aromatic (clove) groups. There has been a significant amount of interest and research into this treatment modality since that initial study. This review identified 22 studies examining OT for olfactory loss (three meta-analyses, two systematic reviews, four RCTs, four prospective randomized trials, two prospective pseudorandomized studies, and seven prospective cohort studies) (Table IX-29).

Benefit with OT has been reported in patients with PTOD, PIOD, and IOD, as well as with OD related to PD 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[1756] performed a retrospective pooled analysis of eight previously published studies. They found an adjusted odds ratio of 0.29 for PTOD and 0.18 for IOD versus PIOD. Patients with PIOD have an odds ratio of 2.77 of achieving a minimum clinically important difference (MCID) on olfactory testing versus control.[1757] A shorter duration of olfactory loss has also been associated with greater recovery with OT in several studies.[1758–1760] Haehner et al[1761] found, in a prospective cohort study with COT for 12 weeks, in patients with PD an improvement on TDI and on threshold for the four scents used for training. Last, Lamira et al[1762] found that OT in adults with age-related olfactory loss (mean age, 66 years) showed a clinically significant improvement in olfaction in 44% of patients who completed the study, but the investigation had a dropout rate of 45%. Two systematic reviews concluded that improvement is primarily in the discrimination and identification realms.[1763,1764]

Most studies have performed OT using four different odors, with the majority using the COT technique, but the odors used do not appear to have a significant effect on outcome.[1755,1757] Patel et al[1765] reported that OT with nonstandardized concentrations of commercially available essential oils was as effective as prior studies using pure odorants, achieving an MCID in 32% of patients (versus 10% of controls). Altundag et al[1766] noted incremental improvement in olfactory recovery in patients with PIOD when using three different sets of four odors for training versus COT for 36 weeks. Conversely, Saatci et al[1767] compared the modified OT method with an OT ball containing the same odors as in COT but found greater improvement with the OT ball. Oleszkiewicz et al[1768] used three different training regimens (COT, four scent mixtures, and three sets of four 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[1769] compared the use

TABLE IX-27 Systematic review of systemic steroid treatments

Author	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Yan, et al[1749]	2019	2	Systematic EBRR	Patients with olfactory loss treated with systemic steroids, topical steroids or both	Studies included only objective psychophysical test confirmation of smell loss (eg, UPSIT®, SS-TDI)	There is weak lower-level evidence only to support use of systemic steroids to treat nonsinonasal inflammatory causes of OD, and their use should be balanced against their known potential side effects and adverse events
Fujii et al[1765]	2002	4	Prospective, single-arm	Population: 27 trauma patients Severity of smell loss: 61% (16) anosmia, 19% (5) severe hyposmia, 11% (3) moderate hyposmia, 8% (2) mild hyposmia Duration of loss: <2 months to >120 months Treatment: dexamethasone injection 4 mg/0.5 mL septal mucosa every 2 weeks × 8	Follow-up: 4 months T&T olfactometer Alinamin test	35.3% improvement in recognition and 23.5% improvement in detection thresholds by T&T olfactometer Patients treated <2 months after trauma had higher rates of improved recognition and detection
Fukazawa et al[1766]	2005	4	Prospective, single arm	Population: 133 URI patients Severity of smell loss: ≈70% severe hyposmia/anosmia Duration of loss: NA Treatment: dexamethasone or betamethasone (5 mg) injection every 2 weeks × 8 to 10 times	Follow-up: NA T&T olfactometer, VAS	49.6% improvement in olfaction threshold recognition by at least 1 patient by T&T olfactometer VAS improved from 10.2 to 39.5
Ikeda et al[1769]	1995	4	Retrospective case series	Population: 9 URI patients Duration of loss: 1 month to 15 months Treatment: failed topical beclomethasone, oral prednisolone 40 to 60 mg × 10 to 14 days with taper	Follow-up: NA T&T olfactometer	No statistically significant improvement in olfaction detection or recognition by T&T olfactometer
Jiang et al[1767]	2010	4	Prospective, single-arm	Population: 116 trauma patients Severity of smell loss: all anosmic Duration of loss: 1 to 264 months Treatment: prednisolone × 15 days starting at 60 mg with taper every 3 days	Follow-up: 3 to 21.5 months (mean 5.5 months) PEA threshold test	16.4% (19 of 116 patients) PEA threshold improved Younger patients more likely to improve in olfaction ($P = 0.033$) No difference in interval of olfactory loss between patients who showed improvement and those who did not ($P = 0.88$)

(Continues)

TABLE IX-27 (Continued)

Author	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Jiang et al[1770]	2015	2 (<80% follow-up)	RCT	Population: trauma, 34 treat/37 controls Severity of smell loss: all anosmic Duration of loss: 0.5 to 180 months Treatment: Prednisolone (1 mg/kg per day taper for 2 weeks) No treatment Zinc Zinc with prednisolone	Follow-up: 3 to 15.5 months (mean 5.6 months) PEA threshold test	4 of 34 (11.8%) improved with steroid vs 1 of 37 improved (2.7%) in the no treatment group (not statistically significant) Younger patients more likely to improve (P = 0.007)
Schriever et al[1768]	2012	4	Retrospective case series	Population: N = 204: idiopathic (n = 157), URI (n = 27), trauma and other (n = 20) Severity of smell loss: Mixed Duration of loss: mean 67±76 months Treatment: 40 mg methylprednisolone × 14 days with taper	Follow-up: 2 visits SS-TDI	All causes 26.6% clinically significant improvement (≥6 TDI patients), mean TDI improvement 3.25 points Idiopathic etiology: 12.1% clinically significant, mean TDI improvement 1.0 point URI etiology: 29.6% clinically significant improvement, mean TDI improvement 4.5 points
Stenner et al#[1750]	2008	4	Retrospective case series	Population: 73 all non-CRS causes Severity of smell loss: mixed, details NA Duration of loss: 2 to 520 months (mean 55 months) Treatment: All patients treated with oral beclomethasone 15 mg every day × 20 day taper After 12 weeks, patients treated with topical budesonide 1.5 mg twice daily or budesonide + neomycin 7.5 mg every day Follow-up: 20 days (after oral steroids only) Olfactory measurement: SS	Follow-up: 20 days (after oral steroids only) SS-TDI	Oral steroids improved mean TDI from 15.5 to 18.7 (P<0.001), 27% had clinically meaningful improvement (≥ 6 TDI patients) Topical treatment did not further improve TDI overall 18.7 to 18.9 patients, 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.
CRS = chronic rhinosinusitis; EBRR = evidence-based review with recommendation; LOE = level of evidence; NA = not available; OD = olfactory dysfunction; PEA = phenylethyl alcohol; RCT = randomized controlled trial; SS = Sniffin' Sticks; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; TDI = threshold, discrimination, and identification; UPSIT® = University of Pennsylvania Smell Identification Test; URI = upper respiratory infection; VAS = visual analog scale.

TABLE IX-28 Systematic review of systemic steroid with or versus topical steroid treatment

Author	Year	LOE	Study design	Study design	Clinical end point	Conclusions
Heilmann et al[1774]	2004	4	Retrospective case series	Population: 55 oral/37 topical URI or idiopathic Duration of loss: 3 to 360 months Treatment: oral prednisolone 40 mg × 21 day taper 2 Mometasone spray daily × 1 to 3 months	Follow-up: 21 to 330 days SS-TDI	All TDI improved with systematic steroids ($P<0.0001$), both URI ($P = 0.05$) and idiopathic ($P = 0.008$) Mometasone spray did not improve OF For both topical and systemic steroids, no difference in olfactory improvement based on patient age, duration of disease, sex, or parosmia
Ikeda et al[1773]	1995	4	Retrospective case series	Population: 5 oral/12 topical trauma Duration of loss: improved patients mean: 72.3 months Unimproved patients: 22.4 months (no significant difference) Treatment: oral prednisolone 30 to 60 mg × 10 to 14 days taper Topical betamethasone twice daily	Follow-up: 6–12 mo. T&T olfactometer, intravenous olfaction test (thiamine propyl)	3 of 5 patients improved from oral steroid in T&T olfactometer and IV testing, 1 of 12 improved from topical steroid treatment
Kim et al[1772]	2017	4	Retrospective case series	Population: 374 URI, trauma, xerostomia, congenital, or idiopathic Duration of loss: mean 78.4 months Treatment: Oral prednisolone 40 mg × 14 days with taper by 5 mg every day Topical Nasonex, 2 sprays in each nostril (total, 200 mg/day) Systemic + topical	Follow-up: 1 month Olfactory measurement: CCCRC olfactory test, B-SIT, subjective "recovery" vs "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[1771]	2009	3	Randomized, nonblinded, parallel group	Population: 28 one arm/43 second arm URI Duration of loss: mean 3.4 months Treatment: All taking mometasone NS Prednisolone × 2 weeks tapering from 30 mg daily Prednisolone × 2 weeks + ginkgo biloba × 4 weeks	Follow-up: 4 weeks Olfactory measurement: BTT, B-SIT	With prednisolone + mometasone spray, 32% had improved BTT score (≥3 points), mean 1.4 points, and 14% had improved B-SIT (≥3 points) mean 0.9 points Both BTT and B-SIT improved $P<0.001$ No statistically significant difference between steroids alone and steroids + ginkgo biloba

B-SIT = Brief Smell Identification Test; BTT = Butanol Threshold Test; CCCRC = Connecticut Chemosensory Clinical Research Center; LOE = level of evidence; NS = nasal spray; OF = olfactory function; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; T&T = Toyoda and Takagi; URI = upper respiratory infection.

of a single scent (phenylethyl alcohol) 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 phenylethyl alcohol thresholds. Poletti et al[1770] 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[1771] used six odors (anise, lemon, rose, vinegar, smoke, and eucalyptus) for OT in patients with PTOD and noted a significant improvement in n-butanol threshold. Last, Qiao et al[1772] found an equivalent recovery in patients with PIOD when COT was compared with 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 to 16 weeks, other studies have found that prolonged duration of OT may have increased incremental benefit. Konstantinidis et al[1773] demonstrated rapid improvement in both short- and long-term training groups in the first 4 months, with a

TABLE IX-29 Use of OT to treat OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Kattar et al[1178]	2020	1	Systematic review and meta-analysis	OT for PIOD 16 studies included 4 in meta-analysis	SS-TDI	All studies reported clinically significant results after OT OT had an odds ratio of 2.77 of achieving MCID vs control
Sorokowska et al[1784]	2017	1	Systematic review and meta-analysis	13 studies	SS-TDI	Strong significant relationship with OT and discrimination and identification, and overall TDI score improvement PIOD has the strongest relationship with improvement
Pekala et al[1785]	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 improved, but not threshold Odds ratio of MCID 2.75
Hura et al[1780]	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[1796]	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[1792]	2018	2	Prospective, RCT	42 patients with PTOD OT with 6 odors for 12 weeks (n = 21) Controls (n = 21)	UPSIT® BAST-24 n-butanol threshold VAS	No significant difference in UPSIT®, BAST-24, VAS 26% vs 5% met MCID for n-butanol threshold at 12 weeks, but not sustained at 24 weeks
Patel et al[1786]	2017	2	Prospective, RCT	43 patients with PIOD or IOD for >12 months OT with 4 essential oils for 26 weeks (n = 19) Controls (n = 16)	UPSIT®	32% in OT group (vs 13% in control group) had >10% improvement on UPSIT®
Damm et al[1781]	2014	2	Prospective, blinded randomized controlled multicenter	171 patients with PIOD for 2 to 24 months High concentration COT (n = 70) Low concentration COT (n = 74) Crossover at 16 weeks	SS-TDI 5-point subjective ranking scale	TDI improved by 3.0 in the high concentration group vs 2.8 in the low concentration group at 16 weeks 26% vs 15% met MCID 53% vs 34% subjective improvement at 32 weeks

(Continues)

TABLE IX-29 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Jiang et al[1797]	2017	2	Prospective, RCT	83 patients with PTOD OT with: PEA (42) Mineral oil (n = 39) for 3 months	PEA threshold UPSIT®-TC MRI OBV	PEA threshold: 24% improved in OT group vs 5% in controls No difference in UPSIT® or OBV
Qiao et al[1793]	2020	2	Prospective, randomized	125 patients with PIOD COT (n = 60) Household OT (n = 65) (balm, vinegar, alcohol, rose perfume) for 24 weeks	SS-TDI	TDI improved by 5.7 and 6.6 in groups, with MCID improvement in 41% in both at 6 months Discrimination and identification also improved in both, but no change in threshold
Saatci et al[1788]	2020	2	Prospective, randomized	60 patients with PIOD OT training ball with 4 scents (n = 30) Modified OT (n = 30) (Altundag) for 12 weeks	SS-TDI 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[1790]	2019	2	Prospective, randomized	111 patients with PTOD COT (n = 45) PEA alone (n = 45) for 6 months	UPSIT®-TC PEA threshold MRI OBV	Both groups had improvement in PEA threshold UPSIT® improved in the PEA group (+1.6), but not in COT MRI not different between groups
Oleszkiewicz et al[1789]	2018	2	Prospective, randomized	108 patients with PIOD or IOD 4 odors (n = 30) 4 odor mixtures (n = 23) 3 × 4 odors, changing every 2 months (n = 20) OT done for 4 to 12 months	SS-TDI	No effect of training regimen on recovery Overall, TDI improved for all groups Threshold and identification improved, but not discrimination
Poletti et al[1791]	2017	3	Prospective, pseudorandomized, single-blinded	96 patients with PIOD (n = 70) and PTOD (n = 26) Heavy weight molecule (n = 48) low weight molecule (n = 48) OT for 5 months	SS-TDI PEA threshold	PIOD MCID improvement 3 × PTOD (45% vs 16%) Only difference between heavy weight molecule and low weight molecule odors were found for threshold in PIOD Others NS

(Continues)

TABLE IX-29 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Konstantinidis et al[1794]	2016	3	Prospective, partially randomized, controlled	111 patients with PIOD COT for 16 weeks (n = 36) COT for 56 weeks (n = 34) Controls (n = 41)	SS-TDI Subjective OF	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 subgroup
Choi et al[1798]	2021	3	Prospective cohort	104 patients with PIOD OT with rose, lemon, cinnamon, orange, peach for 12 weeks (n = 40) Controls (n = 64)	Korean SS-TDI VAS	Improvement in TDI of 4.6 vs 2.7 for controls Threshold improved by 2.1 vs 0.7 in controls Identification improved by 1.6 vs 0.8 in controls No difference in discrimination
Gellrich et al[1799]	2018	3	Prospective cohort	30 patients with PIOD 31 normosmic controls COT for 12 weeks	SS-TDI Gray matter volume on MRI	TDI improved by 5.5 with OT Increased volume of gray matter in hippocampus, thalamus, and cerebellum after OT
Hummel et al[1800]	2018	3	Prospective cohort	50 patients with PIOD or idiopathic loss COT for 16 to 24 weeks (n = 23) Controls (n = 27)	SS-TDI EOG	No improvement on overall composite TDI 35% met MCID improvement EOG response to PEA and hydrogen sulfide improved with OT
Altundag et al[1787]	2015	3	Prospective cohort	85 patients with PIOD Three sets of 4 odors (n = 37) 4 odors (n = 33) Controls (n = 15) for 36 weeks	SS-TDI VAS	Changing odors improved recovery vs standard OT 56% met MCID vs 46% vs none in controls (TDI 8.2 vs 6.1 vs 1.7) Improvement seen in discrimination and identification domains VAS 5.6 vs 5.2 vs 2.8
Konstantinidis et al[1779]	2013	3	Prospective cohort	119 patients with PTOD (n = 38) and PIOD (n = 81) COT with 4 odors (n = 72) Controls (n = 47) for 16 weeks	SS-TDI Subjective olfaction	Improvement seen in both groups vs control, more in PIO Improvement seen in discrimination and identification domains (TDI 6.25 vs 1.5 PIOD, 5.1 vs 1.2 posttraumatic olfactory loss) Subjective ratings also improved in OT groups

(Continues)

TABLE IX-29 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Haehner et al[1782]	2013	3	Prospective cohort	70 patients with PD COT (n = 35) Controls (n = 35) for 12 weeks	SS-TDI 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 the OT group
Hummel et al[1776]	2009	3	Prospective cohort	56 patients with PIOD (n = 35), PTOD (n = 7), or IOD (n = 14) COT (n = 40) Controls (n = 16) for 12 weeks	SS-TDI PEA odor thresholds	Significant difference in OT TDI vs controls Thresholds improved, but not discrimintion or identification scores 28% in the OT group met MCID vs 6% in controls

BAST-24 = Barcelona Smell Test-24; COT = classic olfactory training; EBRR = evidence-based review with recommendation; EOG = electro-olfactogram; IOD = idiopathic olfactory dysfunction; LOE = level of evidence; MCID = minimum clinically important difference; MRI = magnetic resonance imaging; NS = not significant; OBV = olfactory bulb volume; OD = olfactory dysfunction; OT = olfactory training; PEA = phenylethyl alcohol; PIOD = postinfectious olfactory dysfunction; PTOD = posttraumatic olfactory dysfunction; RCT = randomized controlled trial; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, and identification; UPSIT® = University of Pennsylvania Smell Identification Test; UPSIT®-TC = Chinese version of the University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

modest further improvement over the following 9 months for those who 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.[1757] Fornazieri et al[1774] found an adherence rate of 88% after 3 months and 56% after 6 months. By making OT more convenient, Saatci et al[1767] demonstrated improved adherence with an OT ball (56% versus 30%) over 12 weeks.

Overall, all 22 studies reported some improvement with OT. 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 an MCID difference. Only four studies had randomized controls, and blinding patients to therapy remains a challenge.

OT for patients with OD

Aggregate grade of evidence: B (Level 1: five studies; Level 2: eight studies; Level 3: nine studies).

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 OT.

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, OT 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: OT 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.

3 | Intranasal sodium citrate

Sodium citrate, a solution licenced and used safely in other body cavities (eg, 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 PIOD[1780] and

TABLE IX-30 Use of sodium citrate to treat OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Panagiotopoulos et al[1807]	2005	3	Prospective observational (n = 31) 1 mL of sodium citrate – citrate acid (3.5 g/140 mL, pH 7.4, osmolarity 298) to both nostrils	Unspecified (16%) Posttraumatic olfactory loss (3%) Nasal surgery (23%) PIOD (58%)	SS-ID (12 odors) Reported side effects	Thirty patients (97%) improved by a mean of 4 points, 74% had subjective improvement lasting 3 hours Itching was the most common side effect
Whitcroft et al[1803]	2016	2	RCT with patients acting as own controls (n = 57) 1 mL of sodium citrate solution (3.5 g/140 mL, pH 7.4, osmolarity 298) to one side	PIOD (12%) Posttraumatic olfactory loss (18%) Sinonasal disease (53%) Idiopathic olfactory loss (18%)	Monorhinal SS-ID and SS test (PEA) 20 to 30 minutes posttreatment Reported side effects	Only increase seen was in PIOD identification scores (mean 2.29 ± 1.89) Nasal discharge was the most common side effect
Philpot et al[1804]	2017	2	RCT comparing bilateral sodium citrate with placebo (n = 55) 1 mL of 9% sodium citrate solution; 0.5 mL to each side of the nose	Idiopathic (36%) Posttraumatic olfactory loss (16%) PIOD (47%)	Threshold improvement for PEA threshold (rose) Threshold improvement for pear, vinegar, methanol Time until best improvement Reported side effects The 4 threshold tests were used at 15-minute intervals over 2 hours to measure any fluctuations in response	32% had threshold improvement for rose, pear, or methanol Peak improvement was seen at 47 minutes; duration 54 minutes Rhinorrhea and sore throat reported
Whitcroft et al[1805]	2017	3	Prospective, single-blind with patients acting as own controls (n = 49) 1 mL of sodium citrate solution (3.5 g/140 mL, pH 7.4, osmolarity 298) to left nostril	PIOD only	Monorhinal SS-ID and threshold (PEA) 20 to 30 minutes posttreatment	No difference in threshold or identification scores posttreatment. Composite score statistically but not clinically significant (+0.9, $P = 0.04$)

LOE = level of evidence; OD = olfactory dysfunction; PEA = phenylethyl alcohol; PIOD = postinfectious olfactory dysfunction; RCT = randomized controlled trial; SS = Sniffin' Sticks; SS-ID = Sniffin' Sticks identification only.

nonconductive olfactory disorders.[1781] Four interventional studies have been identified—two prospective studies and two 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[1782] performed a prospective placebo-controlled trial of monorhinal treatment of sodium citrate versus sodium chloride for patients with olfactory loss (multiple causes, n = 57) and showed improved olfactory threshold and identification only in the PIOD cohort (n = 7). In 2017, Philpott et al[1804] 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 OF using olfactory thresholds lasting between 30 and 120 minutes after application.[1804] In the latter study, the response rate

was 1 in 3 of the treatment group as compared with none in the control group. In a prospective observational study, the duration of effect subjectively reported by patients was 3 hours.[1807] The subsequent study by Whitcroft et al[1806] that looked specifically at PIOD showed an effect on combined threshold and identification scores, but not separately.[1806]

The method of application differed among 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 (≈35° to 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,[1807] patients were instructed to self-administer the sodium citrate using a 2.5-mL syringe in the "head down and forward" position and then to stay there for 1 minute.

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.

Use of sodium citrate to treat OD

Aggregate grade of evidence: B (Level 2: two studies; Level 3: two studies).

Benefit: May improve olfactory performance for short duration (up to 2 to 3 hours), but replication of this result has varied.

Harm: Short-term side effects (up to 30 minutes after application): local irritation of nasal and oropharyngeal mucosa.

Cost: May include the following:

Direct: $16 USD for 500 g of sodium citrate will provide treatment for several months.

Indirect: Time for daily therapy; could perhaps be used three 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 atomizer to apply the solution.

4 | Vitamins and supplements

a. Omega-3

Omega-3 long-chain polyunsaturated fatty acids 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.[1801] Furthermore, omega-3 supplementation has been suggested to be protective against other neurologic insults and degenerative processes, such as Alzheimer or diabetic sensorimotor polyneuropathy, both known pathologies that are associated with OD, as noted in prior sections.[1809,1810] Finally, accelerated functional recovery after peripheral nerve injury was detected among mice transgenically overexpressing omega-3 long-chain polyunsaturated fatty acids.[1811]

There is one prospective RCT examining OF after endoscopic sellar and parasellar tumor resection with omega-3 supplementation.[1812] The 46 patients randomized to 1000 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 postoperatively compared with 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 long-chain polyunsaturated fatty acids in the treatment of postoperative OD. Future research is needed to characterize the role of omega-3 supplementation in other causes 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.[1813] (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 OD from other inflammatory causes. Additional study is needed to evaluate appropriate treatment protocols and the impact of omega-3 long-chain polyunsaturated fatty acids on other forms of OD.

Use of omega-3 for treatment of OD

Aggregate grade of evidence: B (Level 1b: one study; Level 3: two studies).

Benefit: Protection against olfactory loss after endoscopic skull base surgery as well as potentially protective for other causes of smell loss, eg, in an aging population.

TABLE IX-31 Use of omega-3 to treat OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Yan et al[1812]	2020	1b	RCT	87 patients with sellar/parasellar tumors randomized to: Nasal saline irrigation (n = 41) Nasal saline irrigation and omega-3 supplementation (n = 46)	Postoperative UPSIT® at: 6 weeks 3 months 6 months	Omega-3 protective against olfactory loss 6 months following sellar/parasellar surgery (odds ratio, 0.005; 95% CI, 0.003–0.81 [P =0.03])
Mazahery et al[1814]	2019	3*	RCT	117 children with autism spectrum disorder randomized to: vitamin D (n = 31) omega-3 (n = 29) both (n = 28) placebo (n = 29)	Sensory Processing Measure-taste/smell at baseline and 12-month follow-up	Omega-3 long-chain polyunsaturated fatty acids 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 to 0.1 [P = 0.06])
Gopinath et al[1813]	2015	3	Population-based observational cohort	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 aged >60 years with the highest consumption of nuts and fish had reduced odds of olfactory impairment, independent of potential confounding. (adjusted odds ratio, 0.66; 95% CI, 0.44–0.97)

*Level of evidence (LOE) downgraded because of differences in population (pediatric autism) and differences in outcome measures.
FFQ = Food Frequency Questionnaire; OD = olfactory dysfunction; RCT = randomized controlled trial; SDOIT = San Diego Odor Identification Test; UPSIT® = University of Pennsylvania Smell Identification Test.

Harm: Mild side effects, if any, including unpleasant taste, headache, GI symptoms. Should not be used in patients with underlying bleeding disorders or taking 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 taking 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 causes 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 causes 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 causes of olfactory loss. Additional RCTs with expanded causes of olfactory loss are warranted to prospectively evaluate clinical efficacy and treatment regimens.

b. Zinc

Zinc is involved in cell proliferation and is potentially an important element in maintaining OF.[1814] Zinc sulphate was studied by Aiba et al[1815] and Quint et al[1816] in patients with PVOD. 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.[1814–1819] Lyckholm et al[1814] found zinc ineffective, and potentially with an adverse impact, when treating postchemotherapy anosmia in a small placebo-controlled RCT. Jiang et al[1819] found in posttraumatic olfactory loss

increased recovery rates in patients treated with zinc gluconate when compared with controls.[1820]

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.[1820]

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[1821] proposed that it would be unethical to introduce zinc to the interior of the nose.

Use of zinc to treat OD

Aggregate grade of evidence: B (Level 1: one study; Level 2: two studies; Level 3: three studies).

Benefit: In patients with OD, the response rate of symptoms to oral zinc supplements is similar to spontaneous recovery, with no statistically significant improvement, except in one study assessing posttraumatic 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 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 PTOD: option. Oral zinc treatment for non-PTOD: recommendation against. Intranasal zinc treatment: recommendation against.

Intervention: Zinc treatment should not currently be used to treat most patients with OD.

c. α-Lipoic acid

Typically used as a nutritional supplement and antioxidant for diabetic neuropathy, α-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 that may prevent neural damage involving free radicals.

Only one study has examined the use of α-lipoic acid in olfactory loss. Hummel et al[1814] conducted a prospective, unblinded, noncontrolled trial using α-lipoic acid treatment (600 mg daily) in 23 patients with PVOD. After a median of 4 months of treatment, 61% of patients demonstrated some improvement in TDI scores, with 35% improving by >5.5. A weak correlation was seen between age <60 years 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 α-lipoic acid is normally well tolerated, with a small risk of nausea, rash, and liver enzyme elevation at high doses. Patients with DM have a small risk of medication interaction and hypoglycemia. No other study has been completed to support this finding.

Use of α-lipoic acid to treat OD

Aggregate grade of evidence: D (Level 4: one study).

Benefit: Potential improvement in OF (primarily threshold).

Harm: Low risk of hypoglycemia, nausea.

Cost: Minimal $1 USD per day for a 600-mg dose.

Benefits-harm assessment: Not enough data to interpret potential benefit, but relatively low harm.

Value judgments: Not enough evidence exists to support value in use for OD.

Policy level: No recommendation for use of α-lipoic acid to treat OD.

Intervention: More data are needed before clinicians can present this as a beneficial treatment option for their patients.

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,[1823] reported beneficial effect with high-dose systemic vitamin A therapy in 50 of 56 patients. Another study showed that oral substitution of vitamin A at 10,000 μg/day for 4 weeks cured olfactory loss in patients with liver cirrhosis and vitamin A deficiency.[1824] More recently, however, a double-blind placebo-controlled trial by Reden and colleagues[1825] using a more moderate oral dose of 10,000 IU/day for 3 months, reported no significant improvement in olfactory test scores following treatment with oral vitamin A.[1825] Kartal et al[1826] observed a significant improvement in odor identification after a noncontrolled 3-month systemic treatment with isotretinoin (synthetic analogue of vitamin A) in patients with acne. More convincing evidence comes from a retrospective controlled study with local vitamin A application.[1827] The combined therapy of OT with intranasal vitamin A in a dose of 10,000 IU/day for 2 months produced significantly greater improvement compared with pure OT in patients with postinfectious smell loss. Further, an RCT with a similar experimental approach (vitamin A at 10,000 IU/day with OT versus vitamin A versus standard therapy) is currently being performed in Canada with a large number of patients

TABLE IX-32 Use of zinc to treat OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Harless et al[1818]	2016	1	Systematic review	Pharmacological treatments for the management of PVOD 8 articles were included, yielding 563 patients	Most common assessment: SS-TDI	Zinc sulphate did not show significant improvement in both subjective symptom scores and objective scores, including with SS
Jiang et al[1820]	2015	2	Prospective, randomized	Patient cohort: posttraumatic anosmia (N = 145) Zinc gluconate and prednisolone (n = 39) Zinc gluconate (n = 35) Prednisolone (n = 34) No medication (n = 37)	6-month trial PEA threshold testing	The recovery rates of OF in groups 1 and 2 were significantly higher than the recovery rate in group 4 (group 3 also showed recovery, and was not significantly different when compared with groups 1 and 2) Improvement could be attributable to the use of prednisolone rather than zinc
Lyckholm et al[1815]	2012	2	Double-blinded, placebo-controlled, randomized clinical	Postchemotherapy patient cohort (n = 58) Zinc sulphate 220 mg orally twice daily (n = 20) Placebo (n = 21)	3-month follow-up Patient questionnaire using 1 to 100 scale	No statistically significant difference in the 2 study groups in loss or distortion of smell A trend towards nonsignificant worsening in loss of smell over time in the zinc study group
Quint et al[1817]	2002	3	Prospective clinical	Patient cohort: nonconductive olfactory disorders (n = 77) Caroverine 120 mg/day (n = 51) Zinc sulphate 400 mg/day (n = 56)	4-week study SS test (butanol) SS-ID (16 odors)	The use of zinc sulphate did not produce any significant measurable improvement in olfaction
Aiba et al[1816]	1998	3	Retrospective, nonblinded, noncontrolled, parallel group clinical	Patient cohort: sensorineural olfactory loss (postviral, posttraumatic, or unknown) (N = 426) Zinc sulphate 300 mg daily (n = 25) Zinc sulphate plus topical corticosteroids and oral vitamin B (n = 142) Topical corticosteroids and vitamin B (n = 259)	Follow-up time unclear but listed as at least 1 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

(Continues)

TABLE IX-32 (Continued)

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Henkin et al[1819]	1976	3	Double-blinded, crossover	Patient cohort: variety of causative factors for olfactory loss (N = 106) Crossover between placebo and zinc gluconate	6 months Forced-choice, 3-stimulus sniff test	No statistically significant effects of zinc on either taste or smell function were found

LOE = level of evidence; OD = olfactory dysfunction; OF = olfactory function; PVOD = postviral olfactory dysfunction; SS = Sniffin' Sticks; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination.

TABLE IX-33 Use of α-lipoic acid to treat OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Hummel et al[1823]	2002	4	Prospective observational study (n = 23)	Anosmia α-lipoic acid 600 mg daily Hyposmia α-lipoic acid 600 mg daily	Median follow-up 4 months (3–11) SS-TDI	35% had an increase in TDI score by at least 5.5 Threshold only subscore to reach significance Negative correlation with age and improvement

LOE = level of evidence; OD = olfactory dysfunction; TDI = threshold, discrimination, and identification; SS-TDI = threshold, discrimination, and identification.

and different causes of olfactory loss (ie, postinfectious, posttraumatic, and sinonasal) (ClinicalTrials.gov Identifier: NCT03574701).[1828]

Use of vitamin A treatment for OD

Aggregate grade of evidence: C (Level 2: one study; Level 4: four studies).

Benefit: Local topical vitamin A application led to an improvement in OF in patients with postinfectious smell loss, but these are low-evidence studies. The effect was less pronounced in posttraumatic patients, but also present. No benefit was 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 OD 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 (three case series and noncontrolled studies and evidence of a lack of effectiveness in one RCT), so this modality holds no value.

Policy level: Use of local application of vitamin A is an option in patients with postinfectious and PTOD. 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.

e. Toki-shakuyaku-san

TSS, a traditional Japanese herbal drug (combination of six medical plants: Japanese angelicae root, peony root, cnidium rhizoma, aractylodes 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, Labour and Welfare. In recent years, TSS has also been prescribed in Japan for patients with PIOD and has shown efficacy in improving OF, although the studies all have a low LOE. Recent clinical practice guidelines [1829] 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[1830] reported that the treatment of PIOD with TSS resulted in a greater improvement in OF than that seen with intranasal steroid treatment. Uchida et al[1831] 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[1832] also

TABLE IX.34 Use of vitamin A to treat OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Duncan and Briggs[1824]	1962	4	Case series over a period of 15 years with differences in interventions	Patients with olfactory disorders (eg, postinfectious, posttraumatic, idiopathic; n = 56) treated with high-dose systemic vitamin A therapy (injection, tablets, oral emulsion; 50,000 to 150,000 IU/day) for up to 12 weeks	Subjective olfactory improvement	Improvement in odor detection in 50 of 56 patients
Garrett-Laster et al[1825]	1984	4	Descriptive (noncontrolled)	Vitamin A–deficient patients (n = 27) treated with oral vitamin A (10,000 μg/day) for 4 weeks	Pyridine detection and recognition threshold improvement	Significant improvement in olfactory threshold
Reden et al[1826]	2012	2	Double-blind, placebo-controlled, randomized clinical	Patients with postinfectious or posttraumatic olfactory disorder (n = 52) receiving either oral vitamin A at a dose of 10,000 IU/day or placebo for 3 months	SS-TDI improvement	No significant difference between placebo and verum groups regarding the TDI change and subfunction (TDI) change after treatment
Kartal et al[1827]	2017	4	Descriptive (noncontrolled)	Patients with acne (n = 33) treated with oral isotretinoin (0.5 to 0.8 mg/kg per day) for 3 months	Improvement in SS-ID	Significant improvement in odor identification
Hummel et al[1828]	2017	4	Retrospective cohort	Patients with postinfectious (n = 102) or posttraumatic (n = 68) olfactory disorder (n = 170) Treated with topical vitamin A 10,000 IU once daily, for 8 weeks and performing OT for 12 weeks Performing OT for 12 weeks only	Improvement in SS-TDI	OT + vitamin A produced significantly greater improvement compared with training alone, in discrimination score for all patients and in threshold and discrimination in the postinfectious group In the postinfectious group, significantly more patients showed improved general OF with combined therapy compared with training alone

LOE level of evidence; OD = olfactory dysfunction; OF =olfactory function; OT = olfactory training; SS-ID = Sniffin' Sticks identification only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, and identification.

reported that the improvement rate in patients with post–upper respiratory tract infection 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[1833] additionally reported on the time-course of olfactory recovery and the prognostic factors in patients with PIOD treated with TSS. They revealed that the recovery of OF often occurred during the early period, <6 months from symptom onset, but the number of patients with recovery of OF increased for long-term symptoms 24 months after the first visit. This study also reported that residual OF and younger age were prognostic factors for recovery of OF.[1833] 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 these data currently inconclusive.

Use of TSS for the treatment of OD

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

Benefit: Objective olfactory tests revealed the improvement of OF by oral TSS administration. Lack of consideration for spontaneous improvements, lack of control

TABLE IX-35 Use of TSS for the treatment of OD

Study	Year	LOE	Drug	Study design	Study groups	Clinical end point	Conclusions
Miwa et al[1831]	2005	4	TSS	Case series	60 patients with PIOD and PTOD	T&T olfactometer	TSS resulted in a greater improvement in OF than that seen with intranasal steroid treatment
Uchida et al[1832]	2009	4	TSS	Case series	31 patients with OD	T&T olfactometer	43% of PIOD patients who had not responded to intranasal steroids improved with TSS
Ogawa et al[1833]	2010	4	TSS	Case series	30 patients with PIOD	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[1834]	2020	4	TSS	Case series	82 patients with PIOD	T&T olfactometer	Cumulative olfactory recovery rate at 6, 12, and 24 were 47.3%, 62.7%, and 77.3%, respectively; cumulative olfactory cured rate in the same periods were 23.6%, 33.7%, and 61.0%, respectively; residual OF and younger age were prognostic factors

LOE = level of evidence; OD = olfactory dysfunction; OF =olfactory function; PIOD = postinfectious olfactory dysfunction; PTOD = posttraumatic olfactory dysfunction; T&T = Toyoda and Takagi; TSS = Toki-shakuyaku-san.

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.

Cost: 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 LOE with controlled studies is needed to accurately evaluate the effect of this medication.

Policy level: No recommendation can be made at this time regarding the use of TSS for OD.

Intervention: Well-designed studies using timing restriction for enrollment, controls, and validated measures to obtain higher a LOE is needed.

5 | Minocycline

Minocycline is a second-generation tetracycline antibiotic that has been in use for over 30 years, primarily for the management of acne vulgaris and sexually transmitted diseases.[1829] Minocycline, and the related drug doxycycline, exhibits mechanisms of action beyond their antibacterial 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 CRS.[1836,1837] Both drugs are well tolerated with a low side-effect profile enabling their long-term use in chronic disorders.[1838] Minocycline is also particularly lipophilic with excellent penetration of the CNS; hence, the potential for treatment of neurologic disorders ranging from trauma to neurodegenerative diseases.[1839] These properties suggest that minocycline could play a role in the management of olfactory disorders as well.

TABLE IX.36 Use of minocycline to treat OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Reden et al[1844]	2011	1b	Randomized, prospective, double-blind, placebo-controlled	Patients with PIOD (n = 55) receiving either minocycline (2 × 50 mg/day) or placebo for 3 weeks	Improvement in SS-TDI	Minocycline in the given dosage has little or no effect on the recovery of human OF following postinfectious olfactory loss; however, spontaneous recovery is found in ≈20% of the patients over an observation period of 7 months

LOE = level of evidence; OD = olfactory dysfunction; OF = olfactory function; PIOD = postinfectious olfactory dysfunction; SS-TDI = threshold, discrimination, and identification.

Minocycline was first evaluated as a neuroprotective agent in an animal model of anosmia almost 20 years ago.[1840] This study removed the OB of rats, which reliably produced rapid apoptosis of the peripheral 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.[1841–1843]

Based on this theoretical rationale, as well as an excellent safety profile, a human trial of minocycline for the management of PVOL was undertaken. A total of 55 patients were randomized in a prospective, double-blind, controlled trial of 50-mg 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.[1844] The reasons for failure are uncertain and may be related to the pathophysiology or duration of olfactory loss in postinfectious 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.

Use of minocycline for treatment of OD

Aggregate grade of evidence: B (Level 1b: one 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 PIOD.

Intervention: Minocycline should not currently be offered to patients with OD.

6 | Theophylline

Odorants bind to G-protein–coupled receptors within the OE and trigger an increase in intracellular cyclic adenosine monophosphate. This increase leads to depolarization and a signal transduction cascade to the OB. Phosphodiesterase inhibitors (PDEIs) increase intracellular cyclic adenosine monophosphate and cyclic guanosine monophosphate by preventing their degradation. As such, there is a compelling mechanism by which PDEIs could potentially enhance olfactory signal transduction in patients with OD.

The clinical evidence for PDEIs, however, is mixed. In 2009, an open-label case series by Henkin et al[1835] of 312 hyposmic patients showed that 50.3% of patients had a ≥5% subjective improvement in olfaction after oral theophylline treatment (200–800 mg/day) and 21.7% of these reported that their OF returned to normal. This study was not performed with validated olfaction measures, controls, or strict selection criteria so no definite conclusion can be made. Challenges with oral theophylline, including tolerance and toxicity, with high levels of drug-drug interactions, led to a follow-up open-label case series using topical, intranasal theophylline. This study also showed

TABLE IX-37 Use of theophylline or other PDEIs to treat OD

Study	Year	LOE	Drug	Study design	Study groups	Clinical end point	Conclusions
Levy et al[1852]	1998	4	Oral theophylline 250–500 mg daily	Case series	4 patients with hyposmia (male)	Functional brain activation in response to odorant stimulation	Oral theophylline for 4 to 6 months may improve functional brain activation in response to odorant stimulation
Gudziol et al[1849]	2007	2	Sildenafil 50 mg and 100 mg daily	Double-blinded, placebo-controlled, crossover	20 HCs (male)	SS-TDI	There was a dose-dependent response to 8 days of sildenafil 50 mg had no effect, whereas the 100-mg dose showed decreased objective OF presumably caused by constricted airflow
Gudziol et alet al[1850]	2009	4	Pentoxifylline Intravenous 400 and 600 mg daily	Case series	19 patients with inner ear conditions (6 with hyposmia)	SS-TDI	Significant objective improvement in odor thresholds were seen in patients with hyposmia being treated for unknown duration for inner ear disease
Henkin et al[1845]	2009	4	Oral theophylline 200 to 800 mg daily	Case series	312 patients with hyposmia	Subjective and objective psychophysical measurements	50.3% of patients were responsive to treatment for 2 to 10 months based on >5% subjective improvement
Henkin et al[1853]	2011	4	Oral theophylline 200 to 800 mg daily	Case series	31 patients with hyposmia with available pretreatment and posttreatment 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 to 10 months of treatment
Henkin et al[1846]	2012	4	Intranasal theophylline 20 μg each naris daily	Case series	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[1848]	2016	2	Caffeine 65 mg once	Double-blind, placebo-controlled	76 patients with hyposmia	SS-T and SS-D	Single administration of caffeine had no effect on objective OF

(Continues)

TABLE IX-37 (Continued)

Study	Year	LOE	Drug	Study design	Study groups	Clinical end point	Conclusions
Henkin et al[1854]	2017	4	Oral theophylline 200 to 800 mg daily	Case series	58 patients with hyposmia (n = 44) and HCs (n = 14)	Subjective and objective psychophysical measurements	Objective Shh levels in nasal mucus were associated with subjective improvement in olfaction after 2 to 10 months of treatment
Nigwekar et al[1847]	2017	4	Intranasal theophylline 20 μg each naris daily	Case series	7 patients with ESRD and mild OD	UPSIT®	Intranasal theophylline for 6 weeks yielded minimal objective improvement of odor identification in 5 of 7 patients with ESRD and hyposmia, although below MCID
Stafford et al[1855]	2020	3	Caffeine	Cohort	Coffee consumers (n = 41) and nonconsumers (n = 21) with normal olfaction	Threshold tests for coffee and n-butanol odors	Regular consumers of coffee had an enhanced sensitivity to coffee odor by objective testing
Whitcroft et al[1851]	2020	4	Pentoxifylline oral, 600 mg daily	Case series	6 patients posttraumatic hyposmia	SS-TDI	Oral pentoxifylline for 21 days did not appear to be beneficial in the treatment of hyposmia in this group

cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; ESRD = end-stage renal disease; HC = healthy control; LOE = level of evidence; MCID = minimum clinically important difference; OD = olfactory dysfunction; OF = olfactory function; PDEI = phosphodiesterase inhibitor; SS-D = Sniffin' Sticks discrimination only; SS-T = Sniffin' Sticks threshold only; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; UPSIT® = University of Pennsylvania Smell Identification Test.

improvement in OF in 8 of 10 patients after 4 weeks of treatment, but suffered from the same weaknesses as the prior.[1836] Most recently, in an open-label clinical trial of a very small number of patients with end-stage renal disease and OD, five of seven patients improved with topical, intranasal theophylline (20 μg/day for 6 weeks), although this minimal improvement was below the MCID.[1837]

Theophylline is the most investigated PDEI in the treatment of OD; 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 65 mg of caffeine (eg, espresso) showed no effect on OF.[1838] Additionally, a trial of 20 healthy male volunteers also found no effect of sildenafil on olfaction at 50 mg and, surprisingly, decreased OF was seen at 100 mg, presumably because of nasal congestion.[1839] Furthermore, pentoxifylline administered (intravenously or orally) in 19 patients with otologic conditions demonstrated some improvement in odor threshold scores; however, overall objective olfactory measures did not improve.[1840] Most recently, six patients with posttraumatic hyposmia were administered 200 mg/day of this medication, with some small nonsignificant improvements in odor threshold and identification scores.[1851]

Although there is some Level 2 to 4 evidence to suggest that theophylline may provide subminimally clinical important difference improvement in OF by both oral and topical administrations, definitive conclusions are not able to be made because of limitations in study design. Specifically, these studies do not account for spontaneous olfactory recovery given the lack of a control arm, include a heterogenous group of olfactory loss causes, and rely on subjective assessments rather than validated instruments. PDEIs other than theophylline (eg, caffeine, sildenafil, and pentoxifylline) have not been shown to provide clinically meaningful benefit in patients in the treatment of olfactory loss.

TABLE IX-38 Use of intranasal insulin to treat OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Rezaeian et al[1861]	2018	2	RCT	38 patients with undifferentiated hyposmia for >6 months (36 completed evaluation) Gelfoam with 40 IU insulin (n = 18) Saline-soaked gelfoam (n = 18) placed in OC twice weekly for 4 weeks	Butanol threshold test (0–7) Serum insulin and glucose levels	Very slightly improved olfactory threshold (+1.11 vs −0.02) No change in serum insulin or glucose levels in either group
Schöpf et al[1862]	2015	3	Prospective pilot	Ten patients with PIOD Single dose of 40 IU intranasal insulin (n = 10) Saline 1 year later (n = 7)	SS-TDI Olfactory intensity Hedonic rating	No significant change in TDI score or each individual domain Threshold score minimally improved in 6 patients (+1) Increased intensity score after insulin No change in hedonic rating Strong correlation with BMI and improved olfactory scores with insulin

BMI = body mass index; LOE = level of evidence; OC = olfactory cleft; OD = olfactory dysfunction; PIOD = postinfectious olfactory dysfunction; RCT = randomized controlled trial; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, and identification.

Use of theophylline or other PDEIs to treat OD

Aggregate grade of evidence for systemic PDEIs: C (Level 2: two studies; Level 3: one study; Level 4: six studies).

Aggregate grade of evidence for intranasal theophylline: D (Level 4: two studies).

Benefit: Inconclusive evidence that OF improves with oral or topical administration of PDEIs. Lack of consideration for spontaneous improvements, control populations, and validated assessment tools limit the interpretability of results.

Harm: Described adverse events include restlessness, tachycardia, nausea, anorexia, GI discomfort, and sleep disturbance. These may be less significant with topical administration.

Cost: Low, as the oral PDEIs are available in generic form and FDA approved in other conditions (eg, 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 OD is inconclusive and 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 OD. No recommendation can be currently made regarding use of intranasal theophylline to treat OD.

Intervention: Oral PDEIs should not be recommended in patients with OD 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.

7 | Intranasal insulin

Insulin receptors are found throughout the human body, including the CNS. In the brain, insulin receptors have been noted to be present within the OB, and the

TABLE IX-39 Evidence for platelet-rich plasma injection for the treatment of OD

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Yan et al[1864]	2020	4	Prospective single-arm pilot case series	7 patients with olfactory loss >6 months but <12 months, no evidence of sinonasal inflammatory disease, had failed to improve with OT and topical steroid rinses Single 1-mL PRP injection in bilateral OCs	SS-TDI* at 1 month and 3 months	No adverse events TDI scores improved from mean baseline 19.5 to 23.6 at 3 months Hyposmic patients (16<TDI<30) improved by 5.85 at 3 months, most significantly in the threshold subcomponent 2 patients with anosmia (TDI <16) with no significant improvement Did not control for spontaneous recovery
Mavrogeni et al[1865]	2016	4	Prospective single-arm case series	5 patients with "severe anosmia" without known duration, unresponsive to prior treatment, with no CT abnormalities (1 posttraumatic, 4 postviral 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 patients reported "their smell came back" Mean pretreatment score: 0.19, mean posttreatment score: 4.92 Did not control for spontaneous recovery

CT = computed tomography; LOE = level of evidence; OC = olfactory cleft; OD = olfactory dysfunction; OT = olfactory training; PRP = platelet-rich plasma; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, and identification.

administration of intranasal insulin has been shown to traverse the cribriform plate via olfactory nerves.[1856] However, the effect of insulin on olfaction is not clearly established. Ketterer et al[1857] revealed that creating a hyperinsulinemic state with sustained euglycemia leads to a worsened olfactory threshold (reduced sensitivity) on SS testing (threshold reduced by –1.6) in healthy patients versus fasting controls.[1857] Brunner et al[1858] also demonstrated in a controlled study that a single dose of 40 IU of intranasal insulin in normosmic patients worsened threshold (threshold reduced by –1.3 versus saline) on n-butanol testing but had no effect on discrimination. Conversely, Thanarajah et al[1859] 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 OF.[1860]

Two studies evaluating intranasal insulin for OD were included in analysis (Table IX-38). Rezaeian et al[1861] evaluated the therapeutic effects of intranasal insulin on patients with undifferentiated hyposmia using a double-blinded RCT. An absorbable dressing impregnated with 40 IU insulin or saline was placed endoscopically twice weekly for 4 weeks into the OC. A total of 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[1862] found a similar outcome with a single dose of 40 IU of intranasal insulin in a pilot study of 10 patients with PIOD for >1 year. A total of 60% of the patients had a minimally increased performance in olfactory threshold on SS testing (+1) 30 minutes after application, but TDI and all subdomain 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 OD versus impairment in healthy controls has not been

TABLE IX-40 Studies investigating medical management of phantosmia

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Majumdar et al[1878]	2003	4	Case reports	Sodium valpoate or phenytoin sodium (n = 2)	Subjective improvement (at 3.5 years)	No analysis Symptom resolution
Landis et al[1876]	2010	4	Cohort	Observation (n = 44)	Subjective improvement (at a mean of 6 years)	Phantosmia symptoms: disappeared in 14 (32%), improved in 11 (25%), remained the same in 17 (39%), and worsened in 2 (5%) No association with sex or TDI score
Coleman et al[1880]	2011	4	Cohort	Topirimate, verapamil, nortriptyline, gabapentin (n = 14)	Subjective improvement (at 30 months)	Phantosmia symptoms: improvement in 9 of 14 patients, all patients with headache resolution also had phantosmia resolution
Leopold et al[1879]	2013	4	Cohort	Topical cocaine (n = 6)	Subjective improvement (at 19 months)	Phantosmia symptoms: transient resolution in 5 of 6 patients for hours to days, 1 of 6 patients improved for 6 weeks Phantosmia returned in all patients
Morrissey et al[1877]	2016	4	Cohort	Haloperidol for 3 months (n = 5) Olfactory mucosa excision for failures (n = 3)	Subjective improvement (at 18 months to 5 years)	Resolution of phantosmia in all patients, include 2 of 5 with haloperidol alone and 3 of 5 with surgery
Liu et al[1886]	2020	4	Cohort	OT therapy (n = 43)	SS-TDI (at a mean of 26 weeks)	Presence of phantosmia failed to be associated with clinically relevant improvement in OF

LOE = level of evidence; OF = olfactory function; OT = olfactory training; SS-TDI = Sniffin' Sticks threshold, discrimination, identification combination; TDI = threshold, discrimination, and identification.

established. One proposed theory is increased cyclic adenosine monophosphate and guanosine monophosphate within the olfactory neuroepithelium secondary to intranasal insulin application.[1863]

Use of intranasal insulin to treat OD

Aggregate grade of evidence: C (Level 2: one; Level 3: one).

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 OD is warranted. Limited evidence currently exists.

8 | Platelet-rich plasma

The use of platelet-rich plasma (PRP) as a treatment option for OD has not been well established, but pilot studies have demonstrated safety and potential efficacy.[1856–1858] PRP is an autologous blood product containing supraphysiologic concentrations of platelets with neurotrophic and anti-inflammatory effects that have shown promise in neural regeneration in other peripheral neuropathies.[1859–1872] A murine model of anosmia treated with topical PRP demonstrated improved OF and decreased olfactory epithelial damage.[1873] Two small human studies used PRP for treatment of OD with no adverse outcomes including no worsening smell function.[1864,1865] Most recently, a small case series of patients with recalcitrant olfactory loss (>6 but <12 months) showed statistically significant olfactory improvement at 3 months posttreatment, although the number of patients was extremely limited and there was no control group, so no definite conclusion could be reached.[1864] Although not uniquely targeting patients with

TABLE IX-41 Phantosmia/parosmia surgical treatment options

Study	Year	LOE	Study design	Study groups	Clinical end point	Conclusions
Liu et al[1897]	2020	4	Case report	1 patient with peripheral parosmia underwent OC blocking	Resolution of parosmia Preoperative and postoperative OF	OC-blocking procedure is a novel, simple, safe, and effective procedure for patients with long-term peripheral parosmia
Saltagi et al[1894]	2018	4	Systematic review of retrospective case series	11 patients with phantosmia undergoing medical and/or surgical treatment	Resolution of phantosmia	Two studies looking at surgical intervention were included[9,10] 10 of 11 patients had resolution of symptoms Given the lack of strong evidence to date and risks associated with OC 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[1896]	2016	4	Retrospective case series	3 patients with peripheral phantosmia who failed a 3-month trial of haloperidol underwent endoscopic resection of olfactory neuroepithelium	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[1895]	2002	4	Retrospective case series	8 patients with phantosmia underwent intranasal excision of the OE	Resolution of phantosmia Preoperative and postoperative OF Histologic findings	7 of 8 patients had complete and permanent resolution of their phantosmia Surgical excision is an effective and safe method to relieve phantosmia, but the procedure is technically challenging and carries the risk of CSF leak
Leopold et al[1893]	1991	4	Case report	1 patient with unilateral phantosmia underwent intranasal excision of OE	Resolution of phantosmia Preoperative and postoperative OF Histologic findings	Resolution of phantosmia and return of OF

CSF = cerebrospinal fluid; LOE = level of evidence; OC = olfactory cleft; OE = olfactory epithelium; OF = olfactory function.

OD, treatment of platelet-rich fibrin (second-generation PRP) during septoplasty demonstrated improved olfactory outcomes in the early postoperative period compared with no treatment, with no differences seen at 6 weeks, possibly reflecting the anti-inflammatory effects of PRP.[1866]

PRP has very preliminary potential to improve treatment-resistant OD, particularly for patients 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 multicenter RCT examining multiple injections of PRP versus saline to treat PVOD is currently underway in the United States (NCT04406584).[1874]

Use of PRP injections for treatment of OD.

Aggregate grade of evidence: D (Level 2b: one study; Level 4: two studies).

Benefit: PRP injection represents a safe treatment for OD with early but not well-elucidated potential, particularly for hyposmic patients with persistent smell 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 RCTs 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 OD.

Intervention: PRP injection in the OC is worthy of further investigation for patients with OD without sinonasal disease in whom OT and topical steroid therapy have failed.

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 few studies have investigated medical management of phantosmia and even fewer parosmia.[1864] A small phone interview study of observation alone found that 57% of patients reported short-term improvement of symptoms, while only 32% of patients reported long-term relief.[1865] Medical treatments have been evaluated in small cohort studies with variable success, including antipsychotic medications,[1877] antiseizure medications,[1878] topical cocaine application,[1879] or antimigraine prophylactic medications.[1880] 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 antimigraine prophylactic therapy, including topiramate, nortriptyline, and verapamil. In addition, none of the patients had headache resolution without a corresponding resolution in phantosmia symptoms.[1880]

Medical management of phantosmia lacks large clinical trial evidence and no consensus exists regarding optimal treatment. However, medical therapy for phantosmia may be directed to the underlying etiology, such as antiepileptic therapy for olfactory hallucinations associated with focal epilepsy[1881,1882] or prophylactic migraine medications for migraine-associated phantosmia.[1880,1881] There is some evidence that the distinction between peripheral phantosmia (a dysfunction at the level of the ORs 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.[1875,1877]

OT in which patients sniff numerous scents representing major odor categories[1883] has been discussed as a potential therapy for phantosmia.[1883–1885] A retrospective cohort study of 153 patients with PIOD undergoing OT therapy found that the presence of phantosmia failed to be associated with clinically relevant improvement in OF, but this only points away from phantosmia being a positive predictive factor and does not elucidate whether OT may be helpful for phantosmia itself in some patients.[1886] No clinical trials have been performed on this subject.

Medical management of phantosmia.

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

Of note, this evidence grade is based on the studies listed in the above table. However, because of 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.

2 | Surgical treatment options

The majority of patients with qualitative OD will symptomatically improve or have resolution of symptoms with appropriate medical therapy or observation alone.[1875–1877] 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.[1878–1880] 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[1881] details findings from the first unilateral endoscopic intranasal excision of the OE in a patient with long-lasting phantosmia. Phantosmia initially resolved after excision of the OE and her olfactory ability returned postoperatively. 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 OE in the involved nostrils.[9,10] Postoperatively, phantosmia resolved in 10 of 11 patients. Of the eight patients included in the Leopold et al[9] study, two underwent bilateral surgery and four underwent repeat surgery for persistent symptoms. OF was unchanged in five of the operated nostrils, decreased in three, and improved in two. All patients included in the Morrissey et al[10] study (n = 3) developed anosmia postoperatively. There were no postoperative 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, follow-up is lacking. Additionally, there are serious risks of worsening OF and CSF leak, therefore treatment 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 OC 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.

Surgical intervention for parosmia/phantosmia.

Aggregate grade of evidence: D (Level 4: five 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 OF 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 OC 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 first recommended.

Value judgements: Surgical intervention should only be considered in 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.

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, also known as Kallman syndrome, timely diagnosis and treatment could change the course of the patient's life.[1897]

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.[1898–1900] 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.[1901,1902] 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.

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 OD. We know that polyp status, asthma, DM, and age are all independent predictors of this.[1904] 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 experience olfactory loss from other causes.[1905,1906] 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 OD 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.

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 PVOL, trigeminal chemosensory dysfunction, sudden sensorineural hearing loss, and vocal fold paresis/paralysis.[1904,1905] Pathophysiology of other cranial neuropathies has been shown to involve neuroinflammation, apoptosis, and destruction of neurons, which is similar to PVOL in that it has been documented that neuroinflammation of the olfactory nerves or epithelium leads to neuronal injury and morphological alteration of both the OB and cortex.[1904,1906–5]

Jitaroon et al[6] reported a higher incidence of cranial neuropathies in patients with PVOL than in a control group. Additionally, a family history of neurologic diseases, such as dementia, AD, and stroke, was also shown to be a potential risk factor for having both PVOL 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.

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 OD. 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.[1907,1908] The percentage of patients who reported experiencing a hazardous event related to their smell loss ranged from 22% to 24% for those with mild hyposmia to 39% to 45% with anosmia, three times the rate of those with normosmia.[1907,1908] In addition, patients with impaired olfaction reported concern related to these safety issues, which impacted their QOL.[1909] Olfactory testing was included in the US NHANES of adults, wherein of those aged ≥70 years, 20.3% were unable to correctly identify smoke and 31.3% failed to correctly identify natural gas odor.[1910]

Patients 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 in case of 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 ingesting spoiled food and utilize expiration dates or label foods with dates when storing them.

2 | Nutritional monitoring

Binge-eating disorder is the most prevalent eating disorder, with 2% to 4% of the general population afflicted. While some patients meet criteria of obesity, attacks of binge eating might also occur in patients with AN resulting in weight loss or that are able to maintain a normal weight.[1907]

Sensory influences on food choices may still be underrated despite the sense of smell playing a primary role in flavor perception.[1908,1909] Several additional eating disorders have been associated with altered olfactory capacities.[1910,1911] Alternatively, OD may alter eating behaviors and food appreciation.[1912–1914] In individuals with food avoidance, this disorder might be sensory-related, specifically to aspects of flavor perception (including smell, taste, texture, and color).[1915] While sensory-specific satiety does not seem to be different in patients with OD,[1916] altered eating behaviors in OD may include distortion of food intensity,[1914] decreased pleasure in novel food,[11] over-salting,[12] and tendency to spicy dishes.[1913] Weight gain has been reported for patients with anosmia,

in contrast to weight loss, which is more likely in patients with hyposmia.[1929]

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 the detection of eating alterations with excellent reliability,[1923,1930] future investigators should consider methods used in larger populations regardless of chemosensory function.[1931,1932] Besides 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 4 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 (eg, blood pressure and 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,[1933] 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.[1934] The importance of physical activity, sufficient hydration, and regular sleep should be part of patient management and counseling. Last, in case of a specific eating disorder accompanying OD, in addition to 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 binge-eating disorder.[1917]

3 | Counseling or therapy for psychologic effects

While a number of studies exist evaluating medical treatment (for a review, see Boesveldt et al[1917]), 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 The Individual Burden of OD), this seems striking. The following paragraph thus shortly elucidates available treatment approaches with regard to the psychological effects of OD.

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 peformed to assess subjective suffering and impairments of categorical life areas in order to capture different aspects of mental health. Therefore, a standardized diagnostic interview (eg, Structured Clinical Interview [SCID][1936]) can be performed. The individual diagnoses then should be treated with evidence-based psychotherapeutic interventions (eg, for depressive disorders[1937]). 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 to: (1) evaluate the extent of individual impairment, and (2) develop suitable strategies for detachment processes, eg, gaining acceptance of the situation. The individual significance of olfaction can be assessed by a questionnaire,[1938] 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[1938] as currently used by the patient to ensure adaptive adjustment to the deficits.[1940] Many patients with olfactory disorders exhibit adequate emotionally focused coping strategies, eg, "trying to make the best of the situation" or "comparing one's problems with those who are worse off,"[1939,1941] as well as gradually attributing less importance to the sense of smell in their daily life.[1942] 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, eg, practicing mindfulness,[10,11] are a valuable tool to sustain life quality and self-esteem.[12–14] Beyond that, communication strategies, eg, 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]

XI | SUMMARY OF KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES

A | Etiology

1 | Better delineate cause—many patients still characterized as idiopathic

Current classification of OD is mainly based on the underlying etiology, such as rhinosinusitis, upper respiratory viral infection, and head trauma. If the cause of OD cannot be specified, OD is classified as idiopathic.[1943] The diagnostic modalities for OD include careful history taking, endoscopic inspection of the nasal cavity, CT and MRI, and olfactory tests. Previous studies have demonstrated such diagnostic methods are useful to differentiate idiopathic olfactory loss from the OD of specific causes. For example, CT imaging is useful for the diagnosis of OD associated with rhinosinusitis.[1944,1945] MRI is useful to diagnose OD

caused by skull base disease.[1946] MRI is also useful to evaluate olfactory sulcus depth, OBV, and bulb and nerve morphologies, which may provide diagnostic information on different causes of OD.[1947] However, it is sometimes difficult to exclude the possibility of OD because of 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.[1948] Future improvement in testing methods using new technologies such as radioisotope transport,[1949] biochemical analysis of olfactory mucus,[1950,1951] and technologies currently in development, may contribute to the establishment of improved classification of OD based on more accurate pathophysiology.

2 | Relative susceptibility and underlying mechanisms

While the variety of insults causing OD are well categorized, different individual responses remain poorly understood.[1959] Among the most common causes of OD are rhinosinusitis, head trauma, presbyosmia, and postviral olfactory disorder. If nasal obstruction is excluded, mechanisms may be considered to be sensorineural, but causes can vary widely. For instance, there is evidence for "wear-and-tear" changes or patches of respiratory metaplasia occurring in the OE in presbyosmia,[1960,3] but related pathology in the OB or cortex may be contributory.[4] Also, mechanisms underlying respiratory metaplasia are not clear: is this caused by failed epithelial reconstitution, or neurogenic exhaustion, and is it permanent? Analogous questions occur with postviral 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.

Knowledge gaps

We need better animal models and understanding of what happens on a cellular level and olfactory system level in nonsinonasal inflammation–related causes of OD.

Rodent models have provided a wealth of knowledge regarding olfaction, yet gaps remain. Disorders thought to result from direct damage to the OE have been modeled in rodents using intranasal chemicals or systemic drugs.[6,7] Following chemical damage, olfactory epithelial reconstitution and axon projection to the OBs 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 modeling.[8] Genetic models to test cell type–specific gene knockout, 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 ORs 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 the causes and to test therapies. Recent rodent viral infection models may improve the understanding of classical postviral 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]

B | Clinical Assessment

1 | How culture and literacy affect some psychophysical test results

a. Developing more clinically accessible, truly objective, quantitative tests

As noted in above, 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.[1961–1965]

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

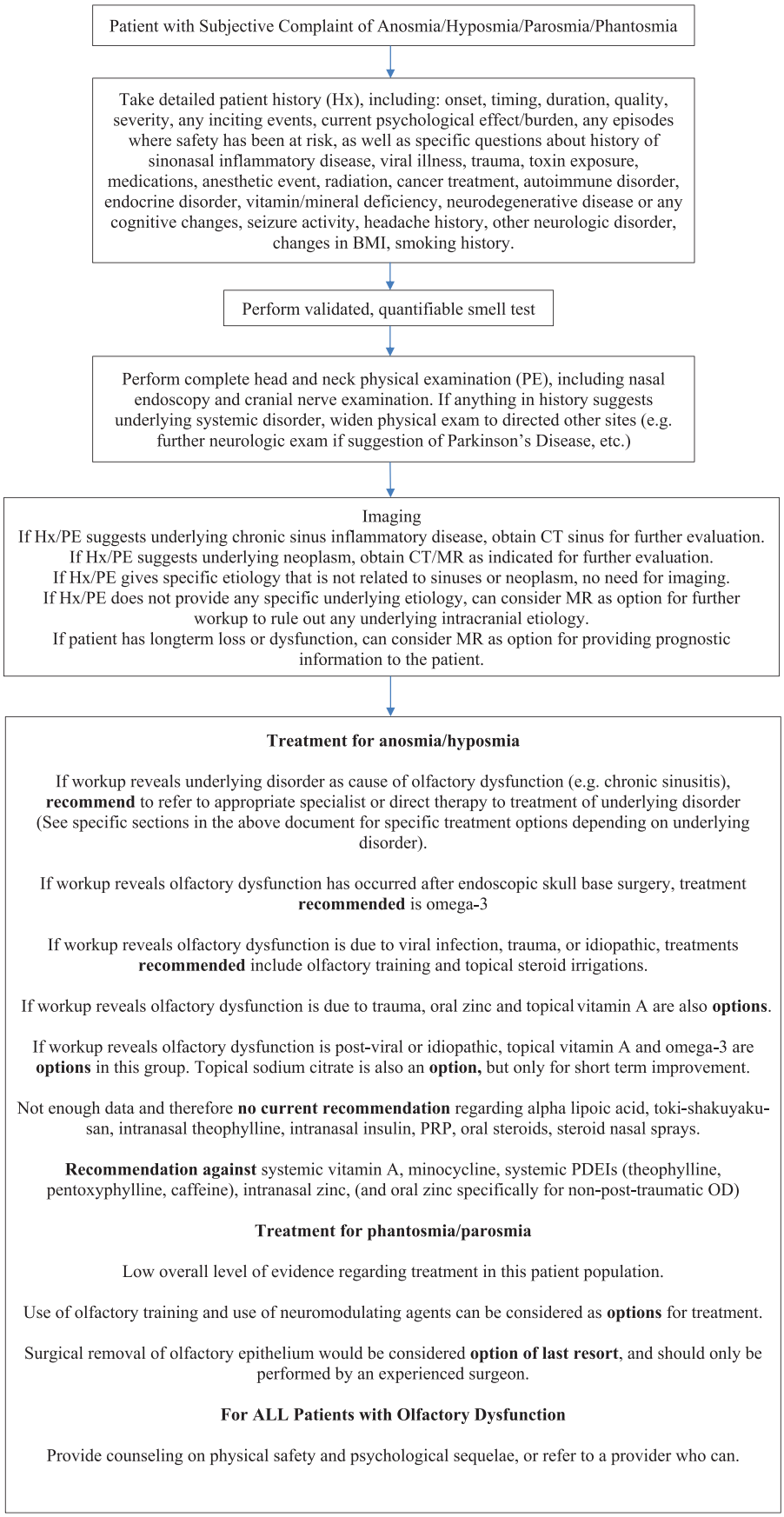

FIGURE XI Algorithm for diagnosis and management of the patient with OD

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.[1966]

Development of simpler quantitative tests

Electro-olfactography and adapted electroencephalography have long been utilized in the research setting to try and provide more olfactory data points that are free from subjective and situational influence.[1967] 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 that is ripe for development, and, simpler yet, universal quantitative testing is already being developed in some centers.[1968]

C | Management

1 | Identify predictors of response to current and future therapeutic options

It would be useful for the management of patients with OD if the efficacy of each treatment option offered to them could be predicted in advance. For example, the OD associated with rhinosinusitis often responds to treatments directed at controlling underlying inflammation, such as 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 OD compared with patients with IOD, especially when comparing with patients with sinonasal disease with nasal polyps.[1975] Other studies demonstrated that success of a trial of systemic steroids may serve to verify that the loss is indeed inflammatory[1976] and is a prognostic indicator for a significant benefit of 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 cutoff point for recovery of smell following ESS.[4] A positive response to an intravenous olfactory test (eg, prosultiamine), absence of OC lesions, female sex, and younger age were also identified as independent prognostic factors for better olfactory outcomes 3 months after ESS.[5]

In PVOD, multivariate analysis showed that younger age and residual OF were significantly associated with better olfactory recovery.[1982] A study in Japan showed that onset latency in the intravenous olfactory test may help predict when olfaction in patients with PVOD will improve.[1983] On the other hand, PTOD or IOD were significantly associated with less possibility of improvements compared with PVOD in patients with OD receiving OT.[1984] Finally, there is a significant correlation between changes in OF and initial measurement of the total OBV, with larger volumes relating to higher improvement of OF, although this does not predict which therapeutic option is best for either group.[1985]

A new methodology, radioisotope transport analysis, has demonstrated that high thallium migration from the nasal cavity to the OB is significantly correlated with better prognosis in patients with OD, suggesting that patients with intact olfactory nerve fibers could be selected to use this imaging technique.[1986]

2 | A "cure" for all olfactory disorders

In all probability, there will not be a single cure for all causes of OD. This is attributable to the fact that olfactory disorders are not one monolithic entity, but instead can be dissected into different fractions,[1977] 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.[1978] Stimulating regeneration of OR neurons,[1979] transplantation of olfactory mucosa, and working to develop stem cell regeneration[1980] or developing olfactory implants[1981] are excellent ideas but may have limited effects on CNS causes of olfactory disorders residing at the level of the OB or the OFC. 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.

3 | Increase public awareness of this disorder and its many implications

Increasing public awareness regarding the importance of OF and OD is significant in terms of empathy and sympathy for patients experiencing 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 frequent and ≈5% of the general population have no functioning sense of smell.[1977] This lack of awareness of OD is probably related to many factors, eg, the gradual decrease of OF 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 COVID-19, with sudden olfactory loss observed in a large number of (also younger) patients, and the appearance of active organizations created by people with chemosensory dysfunction such as Fifth Sense[1978] or Abscent[1979] in the United Kingdom, the Smell and Taste Association of North America (STANA),[1980] or Reuksmaakstoornis in the Netherlands.[1981] 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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