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Position paper on olfactory dysfunction: 2023*

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Abstract

Background: Since publication of the original Position Paper on Olfactory Dysfunction in 2017 (PPOD-17), the personal and societal burden of olfactory disorders has come sharply into focus through the lens of the COVID-19 pandemic. Clinicians, scientists and the public are now more aware of the importance of olfaction, and the impact of its dysfunction on quality of life, nutrition, social relationships and mental health. Accordingly, new basic, translational and clinical research has resulted in significant progress since the PPOD-17.

In this updated document, we present and discuss currently available evidence for the diagnosis and management of olfactory dysfunction. Major updates to the current version include, amongst others: new recommendations on olfactory related terminology; new imaging recommendations; new sections on qualitative olfactory dysfunction (OD) and COVID-19 olfactory dysfunction; and an updated management section. Recommendations were agreed by all co-authors using a modified Delphi process.

Conclusions: We have provided an overview of current evidence and expert-agreed recommendations for the definition, investigation, and management of olfactory dysfunction. As for our original Position Paper, we hope that this updated document will encourage clinicians and researchers to adopt a common language, and in so doing, increase the methodological quality, consistency, and generalisability of work in this field.

Key words: smell, olfaction disorders, therapeutics, investigative techniques

Contents

Abbreviations

ACE2	Angiotensin-converting enzyme 2
AERD	Aspirin exacerbated respiratory disease
ALA	α-linolenic acid
APOE	Apolipoprotein E
AUC	Area under receiver operating characteristic (ROC) curve
BAST-24	Barcelona Smell Test – 24 odours
BID	Twice a day
BOT-8	8-Odourant Barcelona Olfactory Test
B-SIT	Brief Smell Identification Test
C19OD	COVID-19-associated olfactory dysfunction
cAMP	Cyclic adenosine monophosphate
CCAD	Central compartment atopic disease
CCCRCT	Connecticut Chemosensory Clinical Research Center Test
CC-SIT	Cross-cultural Smell Identification Test
CENTRAL	Cochrane Central Register of Controlled Trials
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
COWoG	Clinical Olfactory Working Group
CRS	Chronic rhinosinusitis
CT	Computed Tomography Scan
DHA	Docosahexaenoic acid
EEG	Electroencephalography
ENT	Ear, Nose, and Throat
EOG	Electroolfactogram
EPA	Eicosapentaenoic acid
FESS	Functional endoscopic sinus surgery
fMRI	Functional magnetic resonance imaging
GA2LEN	Global Allergy and Asthma European Network
GBC	Globose stem cells
H2S	Hydrogen sulfide
HAAS	Honolulu Asia Aging Study
HBC	Horizontal stem cells
HIV	Human immunodeficiency virus
IFT88	Intraflagellar Transport 88
IL	Interleukin
IU	International units
KNHANES	Korea National Health and Nutrition Examination Survey
LIFE	LIFE-Adult-Study of the Leipzig Center for Civilization Diseases
LoS	Loss of Smell Scale
MAP	Memory and Aging Project
MCID	Minimal clinically important difference
MCS	Multiple chemical sensitivity, also idiopathic environmental intolerance
MeSH	Medical subject heading
MMSE	Mini-mental State Examination

MRI	Magnetic Resonance Imaging
NAC	N-acetylcysteine
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NSHAP	National Social Life, Health, and Aging Project
OB	Olfactory bulb
OBP	Odorant binding protein
OC	Olfactory cleft
OCES	Olfactory Cleft Endoscopy Scale
OD	Olfactory dysfunction
ODOUR	Olfactory Dysfunction Outcomes Ratings
OE	Olfactory neuroepithelium
OERP	Olfactory event-related potential
OFC	Orbitofrontal cortex
OLFACAT	Olfaction in Catalonia
OR	Olfactory receptor
OSC	Olfactory sustentacular cells
OSN	Olfactory sensory neuron
OT	Olfactory training
pBOT-6	6-Odourant Paediatric Barcelona Olfactory Test
PD	Parkinson's disease
PET	Positron emission tomography
PIOD	Post-infectious olfactory dysfunction
PPE	Personal protective equipment
PROM	Patient-reported outcome measures
PRP	Platelet-rich plasma
PTOD	Post-traumatic olfactory dysfunction
QID	Four times a day
QOD	Questionnaire of Olfactory Disorders
QOD-NS	Questionnaire of Olfactory Disorders-Negative Statements
Q-SIT	3-item Quick Smell Identification Test
RA	Retinoic acid
RAND/UCLA	Research and Development/University of California – Los Angeles
REACT-1	REal-time Assessment of Community Transmission
RNA	Ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome associated coronavirus 2
SC	Subcutaneous injection
SD	Standard deviation
SDOIT	San Diego Odour Identification Test
SIT/SIT-40	40-item Smell Identification Test (previously known as UPSIT)
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SNOT-22	Sino-nasal Outcome Test – 22
SOIT	Scandinavian Odour Identification Test
sQOD-NS	Short version of Questionnaire of Olfactory Disorders – Negative Statements
SR	Steroid responsiveness
SSParoT	Sniffin Sticks Parosmia Test
T&T	Toyota & Takagi Olfactometer
TDI	Threshold, Discrimination, Identification Score, as in extended "Sniffin' Sticks" Olfactory Test

TID	Three times a day
TMPRSS2	Transmembrane serine protease 2
UK	United Kingdom
UPSIT	University of Pennsylvania Smell Identification Test
UPSIT-TC	UPSIT Traditional Chinese Version
URTI	Upper respiratory tract infection
US/USA	United States of America
UV	Ultraviolet
VAS	Visual analogue scale
WMD	Weighted mean difference

Executive summary

Since publication of the original Position Paper on Olfactory Dysfunction in 2017 (PPOD-17), the personal and societal burden of olfactory disorders has come sharply into focus through the lens of the COVID-19 pandemic. Clinicians, scientists and the public are now more aware of the importance of olfaction, and the impact of its dysfunction on quality of life, nutrition, social relationships and mental health. Accordingly, new basic, translational and clinical research has resulted in significant progress since the PPOD-17. However, the overall quality of evidence, particularly for the management of olfactory dysfunction (OD), continues to lag behind that of other sensory impairments.

In this updated document, we present and discuss currently available evidence for the diagnosis and management of olfactory dysfunction. Major updates to the current version include:

1. New recommendations on olfactory related terminology.
2. New sections on qualitative olfactory dysfunction (parosmia and phantosmia), including pathophysiology, assessment, and treatment.
3. New section on COVID-19-related olfactory dysfunction, including clinical presentation and pathogenesis.
4. New imaging recommendations according to underlying aetiology.
5. Updated management section – including new medications such as biological therapies as well as updates on research related to olfactory training and surgery. Summary evidence is now presented in table form according to aetiology.
6. New section on novel treatments including research on: vitamin A; olfactory implants; stem cell therapies; gene therapy; platelet-rich plasma; omega-3 fatty acids; N-acetylcysteine, and other treatments.
7. New section on unmet needs and future research.

The recommendations found within this document were agreed by all co-authors using a modified Delphi process. Recommendations and key points can be found in the summary below.

Summary of contents

Terminology

Heterogeneity in olfactory related terminology is still present in the literature. We recommend terminology in keeping with the recently published consensus statement from the Clinical Olfactory Working Group (Hernandez et al., 2022), as outlined in Table 1. Most notably, the term 'functional anosmia' is replaced with 'anosmia'.

Table 1. Definitions of terminology used in olfactory research/practice.

Normosmia	Quantitatively normal olfactory function
Hyposmia (or 'microsmia')	Quantitatively reduced olfactory function.
Anosmia	Quantitatively reduced olfaction to the extent that the sense of smell is not useful in daily life
Specific Anosmia (or 'partial anosmia')	Quantitatively reduced ability to smell a specific odour despite preserved ability to smell the vast majority of other odours.
Hyperosmia	Quantitatively increased ability to smell odours (>90th percentile of scores in an olfactory test)
Olfactory intolerance	Qualitative olfactory dysfunction where individuals, without odor distortions, complain of a subjectively enhanced sense of smell and are intolerant of everyday odors
Parosmia	Qualitative dysfunction in the presence of an odourant (i.e., distorted perception of an odour stimulus).
Phantosmia	Qualitative dysfunction in the absence of an odourant (i.e., an odourant is perceived without concurrent stimulus, an 'olfactory hallucination').
Orthonasal olfaction	The perception of odourants anteriorly due to airflow from the nostrils to the olfactory clefts, e.g., during sniffing.
Retronasal olfaction	The perception of odourants located within the oropharynx, caused by airflow to the olfactory clefts via the nasopharynx during swallowing or nasal exhalation.

Recommendation:

➢ We recommend the use of the terms highlighted in bold in the above table, with their associated definitions.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)

Epidemiology of olfactory dysfunction

Estimated prevalence rates vary according to assessment technique and sample population. It is therefore important that studies are interpreted and planned with this in mind. The prevalence of olfactory dysfunction increases with age. Idiopathic dysfunction in older adults is linked with cognitive decline and increased risk of mortality. Other factors, such as male gender, smoking and race/ethnicity have been linked to dysfunction in some, but not all studies.

Key Points:

- Estimates of olfactory dysfunction prevalence vary with assessment method and should ideally be determined using a validated psychophysical tool for the population in question,

in addition to subjective reporting.
- Meta-analytic work demonstrates that olfactory dysfunction affects approximately 22% of the general population [46].
- Normal aging significantly contributes to this burden.

Anatomy and physiology of olfaction

Except for in rare cases, olfactory perception requires intact peripheral and central systems. Peripherally, olfactory sensory neurons are found within the neuroepithelium of the olfactory cleft, and following activation by odourants, transmit signals via their axons (collectively CN I) to the olfactory bulb. Following signal integration at the level of the olfactory bulb, further processing occurs within structures of the primary and secondary olfactory networks.

Key point:
- Olfactory sensory neurons are prone to damage due to their exposed position but are capable of regeneration from stem cells found within the olfactory neuroepithelium.

Causes and classifications of olfactory dysfunction

There are many possible underlying causes of olfactory dysfunction. The most common of these are (excluding dysfunction related to age): sinonasal disease (including CRS, particularly in Type-2/CRSwNP), post-infectious olfactory dysfunction, post-traumatic olfactory dysfunction and dysfunction related to neurological diseases. Idiopathic olfactory dysfunction is a diagnosis of exclusion, that should only be made after exhaustive work up.

Recommendation:

➢ Classification of olfactory dysfunction should be according to underlying aetiology (e.g., post-infectious, post-traumatic etc).

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

➢ Idiopathic olfactory dysfunction is a diagnosis of exclusion that should only be made following careful assessment, including normal MRI and exclusion of underlying inflammatory pathology.

o Delphi result: Agreed (score 7-9 = 93.5%, average score 8.5)

Qualitative olfactory dysfunction

Parosmia and phantosmia are the most common types of qualitative olfactory dysfunction, and can have significant impact on quality of life and nutrition. The pathophysiology of such dysfunction has not yet been fully delineated, and may involve both peripheral and central elements. At present, the evidence base for treatment of qualitative dysfunction is poor, limiting possible recommendations on their use.

Recommendation:

➢ The presence of parosmia or phantosmia, and their potential underlying causes, should be established through careful medical history.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)

➢ Structured symptom questionnaires, severity scores, and psychophysical olfactory tests may be used as adjuncts to diagnosis.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

➢ Due to their frequency of co-occurrence, assessment for quantitative olfactory dysfunction should be undertaken when qualitative dysfunction is reported.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

➢ Imaging in qualitative dysfunction may be of use where there is suspicion of an endogenous odour source, or central pathology.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.6)

➢ Where a neurological or psychiatric cause is suspected, appropriate specialist input should be sought.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.8)

Clinical assessment

Thorough assessment of olfaction includes the medical history, clinical examination, chemosensory testing ± structural imaging. With regards to these, we make the following recommendations:

Recommendation:

History

➢ Thorough clinical histories should be sought from all patients.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.9)

Examination

➢ Patients with suspected olfactory dysfunction should undergo a full ENT examination, including nasal endoscopy with careful inspection of the olfactory cleft.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.8)

➢ Basic neurological examination should be undertaken where there is suspicion of an underlying neurological aetiology, or in otherwise assumed idiopathic cases, though formal and detailed neurocognitive testing can be deferred to the appropriate specialists.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.7)

Subjective olfactory assessment

➢ In patients reporting olfactory dysfunction, subjective olfactory assessment should be undertaken in order to fully determine quality of life and disease burden, as well as the clinical impact of interventions.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.6)

➢ When possible, validated questionnaires should be used. When this is not possible, a recognised form of assessment, possibly quantitative and/or anchored, such as a visual analo-

gue scale, should be used.
o Delphi result: Agreed (score 7-9 = 96%, average score 8.5)
➢ Subjective olfactory assessment should not be relied upon in isolation.
o Delphi result: Agreed (score 7-9 = 91%, average score 8.4)

Psychophysical olfactory assessment: general
➢ Psychophysical olfactory assessment tools should be reliable and validated for the target population.
o Delphi result: Agreed (score 7-9 = 98%, average score 8.8)
➢ Psychophysical olfactory assessment tools used in clinical and research settings should include tests of odour threshold, and/or one of odour identification or discrimination. However, we strongly encourage to test olfactory function by including two or three of these subcomponents.
o Use of other suprathreshold olfactory testing modalities can be considered, where such tests have been validated and have sufficient normative data.
o Delphi result: Agreed (score 7-9 = 91%, average score 8.3)

Psychophysical olfactory assessment: children
➢ When testing olfaction in children, the test should fit the motivation of the child, be culturally appropriate, and validated for the target age.
o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

Psychophysical olfactory assessment: use for diagnosis of impairment
➢ Definitions of olfactory impairment should only be made with reference to normative values for the psychophysical olfactory test being used.
o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)
➢ Psychophysical olfactory testing should ideally begin with monorhinal odour threshold testing, if feasible. Where there is no significant difference in lateralised scores, testing may continue birhinally.
o Delphi result: Agreed (score 7-9 = 70%, average score 7.2)

Psychophysical olfactory assessment: use to define clinically relevant change in olfactory function
➢ When reporting changes in psychophysical olfactory test scores, improvement or deterioration in olfactory function should be defined according to established clinical correlates and target population for that olfactory test.
o Delphi result: Agreed (score 7-9 = 96%, average score 8.5)

Psychophysical olfactory assessment: screening
➢ Screening for abnormal olfactory function in asymptomatic patients should be undertaken using validated psychophysical olfactory tools.
o Delphi result: Agreed (score 7-9 = 89%, average score 8.2)
➢ Patients with abnormal screening results should undergo full olfactory testing.
o Delphi result: Agreed (score 7-9 = 96%, average score 8.5)

Psychophysical olfactory assessment: home tests
➢ When formal psychophysical olfactory testing is not possible (for example, in acutely infectious COVID-19 patients), validated home smell tests may be of use.
o Delphi result: Agreed (score 7-9 = 94%, average score 8.3)
➢ Patients with abnormal results should undergo full olfactory testing.
o Delphi result: Agreed (score 7-9 = 94%, average score 8.5)

Retronasal olfactory and gustatory testing
➢ Comprehensive psychophysical assessment should include gustatory screening for sweet, salty, sour, and bitter tastes in all cases.
o Delphi result: Agreed (score 7-9 = 80%, average score 7.7)
➢ Full gustatory testing should be performed where abnormalities are identified on screening or where it is not possible to differentiate between impaired gustation and retronasal olfaction. Accordingly, this should ideally include discrimination between retronasal olfaction (flavours) and gustatory (taste) abnormalities.
o Delphi result: Agreed (score 7-9 = 89%, average score 7.9)

Electrophysiology and functional imaging
➢ Whilst electrophysiological and imaging studies are often reserved for research purposes, EEG-based olfactory testing can be useful for medico-legal purposes.
o Delphi result: Agreed (score 7-9 = 85%, average score 7.9)

Structural imaging
➢ Structural imaging should be undertaken according to suspected underlying aetiology (Table 6).
➢ In idiopathic olfactory dysfunction: CT of the paranasal sinuses is optional and may identify inflammation not otherwise diagnosed by endoscopy or trial of corticosteroids; MRI brain is recommended.
o Delphi result: Agreed (score 7-9 = 91%, average score 8.3)

➢ CT should be performed as first line imaging of the paranasal sinuses when sinonasal inflammation or bony abnormalities are suspected. MRI should be performed as first line when intracranial abnormalities are suspected, or morphometry of the OB is required.
o Delphi result: Agreed (score 7-9 = 98%, average score 8.8)

A suggested approach to assessment and management of olfactory dysfunction can be found in Figure 4. A summarised basic version of the assessment arm can be found in Figure e1.

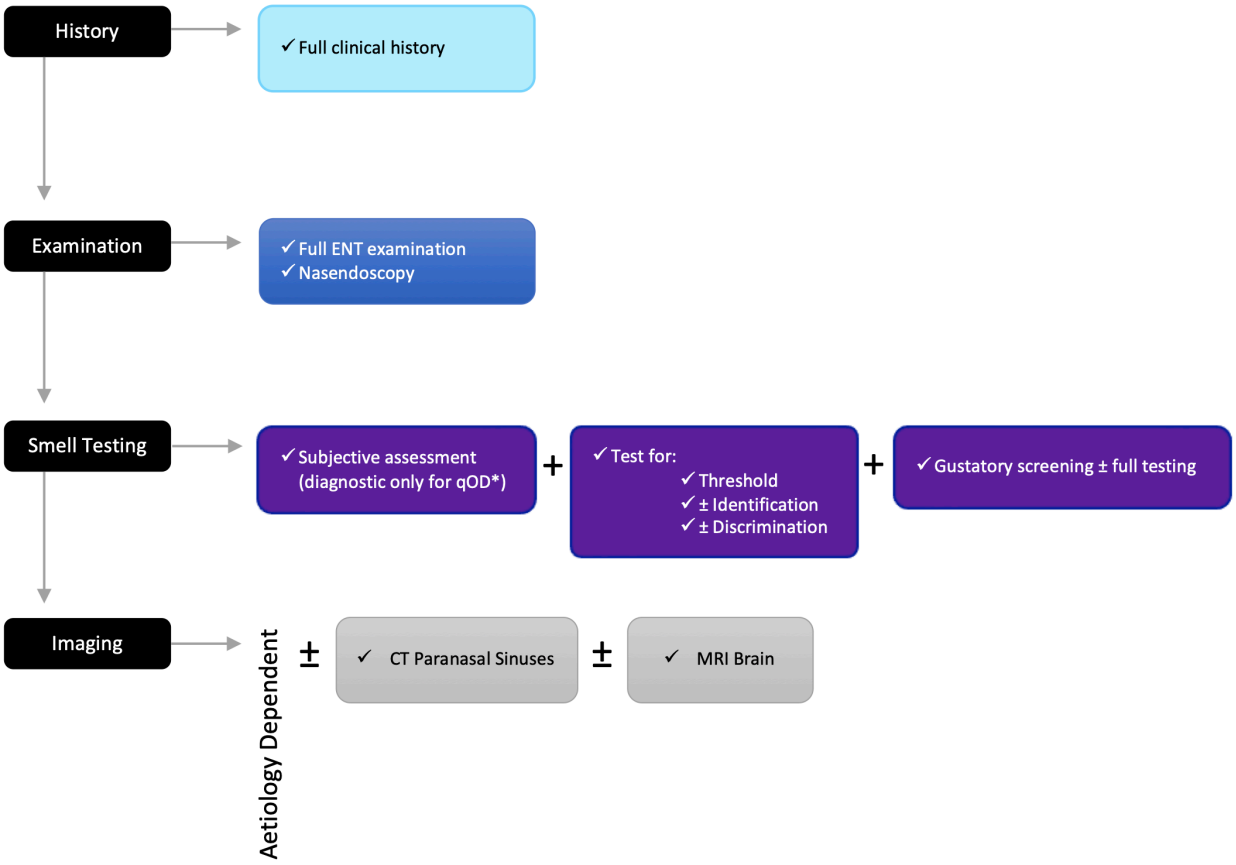

Figure e1. Basic summary flowchart of clinical assessment (for full flowchart see Figure 4).

Treatment of olfactory dysfunction

Despite considerable efforts within both the clinical and research communities, long-term, effective treatments for OD largely remain elusive. The current evidence base is limited by lack of high-level evidence. Recommendations regarding the following treatments have been made:

Recommendations:

Corticosteroids

➢ Systemic (short courses) and/or intranasal (long-term) corticosteroids should be prescribed in patients with olfactory dysfunction secondary to CRS, severe allergic rhinitis, and other inflammatory conditions according to existing clinical guidelines.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)

➢ There is limited evidence to support use of systemic or intranasal corticosteroids for other causes of olfactory dysfunction, but if topical steroids are used, a delivery mechanism that can reach the olfactory cleft (i.e., rinses in place of sprays) would be recommended.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.5)

➢ Potential side effects and contraindications should be taken into account when prescribing systemic corticosteroids.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.9)

Monoclonal antibodies (biologics)

➢ Further research with larger patient cohorts and use of thorough psychophysical olfactory testing is required to fully delineate the effect of monoclonal antibody treatment for CRS-related olfactory dysfunction.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.4)

➢ In severe CRSwNP, biologic treatment appears to improve olfactory dysfunction. Among them, dupilumab seems to be the most effective. However, we would refer you to existing guidelines on the treatment of CRS for use of these medications.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.6)

Phosphodiesterase inhibitors

➢ Currently, there is insufficient clinical evidence to support the use of phosphodiesterase inhibitors in the treatment of olfactory dysfunction for any underlying aetiology.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.5)

Intranasal calcium buffers

➢ Currently, there is insufficient clinical evidence to support

the use of calcium buffers, in the treatment of olfactory dysfunction for any underlying aetiology.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.5)

Olfactory training

➢ Olfactory training can be recommended in patients with olfactory loss due to several aetiologies, such as PTOD and PIOD. However, this treatment requires further evaluation in patients with sinonasal inflammatory disease and neurodegenerative diseases.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

Surgery

➢ Functional endoscopic sinus surgery for olfactory loss caused by the chronic rhinosinusitis disease spectrum should be undertaken in line with existing guidelines, and is not recommended for olfactory dysfunction without associated chronic rhinosinusitis.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.6)

➢ There is presently insufficient evidence to support other surgery types for olfactory dysfunction.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)

Treatment of qualitative olfactory dysfunction

The evidence base for treatment of qualitative olfactory dysfunction is very limited. For the majority of evidence available, qualitative disorders have been included as secondary outcomes of interest. Further research is therefore required.

Recommendations:

Parosmia

➢ A higher level of evidence is required for existing therapies before recommendations regarding their use in the treatment of parosmia can be made.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.6)

➢ Until further evidence is available, treatment of parosmia associated with known quantitative olfactory dysfunction (e.g., PIOD) should be in line with evidence for the quantitative condition.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.5)

Phantosmia

➢ Treatment of phantosmia associated with neurological conditions should be undertaken as for the underlying condition, with appropriate specialist guidance.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.8)

➢ For non-neurological phantosmia, a higher level of evidence is required for existing therapies before recommendations for their use can be made.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.8)

➢ Until further evidence is available, treatment of phantosmia associated with known quantitative olfactory dysfunction (e.g., PIOD) should be in line with evidence for the quantitative condition.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.6)

Novel treatments

Early basic and clinical research for novel treatments is described. These include: vitamin A; olfactory implants; stem cell therapies; gene therapy; platelet-rich plasma; omega-3 fatty acids; N-acetylcysteine; and other treatments.

Recommendations:

➢ Further high-quality research is required for all of the above novel treatments before recommendations for their clinical use can be made.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.7)

Recommendations and Delphi Exercise Summary

A summary of the recommendations made and a discussion regarding those achieving the lowest level of consensus are discussed in this section. As a result of this, one further recommendation was included as follows:

Recommendation:

➢ Increased funding should be made available in order to facilitate chemosensory assessment as outlined in this position paper. Where this is not possible at the local level, clear referral pathways should be established to specialist centres where such assessment can be undertaken, thereby enabling equitable access to care.

Unmet needs and future research

Future basic and translational research would benefit from specific steps, such as the development of immortalised (ideally human) cell lines and organoids, establishing multicentre/international consortia and databases, longitudinal studies, as well as more general shifts in approach, including cross-disciplinary collaboration and training of future clinical scientists. Clinical practice would benefit from increased uptake and consistency in psychophysical testing, international collaboration (through registries, databases and multicentre RCTs) and big data work. Core outcome sets have been proposed with respect to these aims. Finally, integration of patients and participants into all stages of the research process should be encouraged.

Introduction

Since publication of the original Position Paper on Olfactory Dysfunction [1], the olfactory landscape has been radically altered by the emergence of SARS-CoV-2. The global pandemic has created the largest single cohort of acute and post-infectious olfactory dysfunction in history, with some estimates placing the number of patients affected (at time of writing) at several hundred million. In addition to this highly significant burden of disease, COVID-19 has brought olfactory dysfunction to the forefront of public knowledge and catalysed a dynamic body of new research within the ENT and wider community.

With this new clinical and research interest, evidence-based approaches to both the diagnosis and management of olfactory dysfunction are pivotal. Whilst there have been improvements in recent years, heterogeneity in both clinical and research approaches still exist – made worse by the challenges of safe olfactory assessment during times of pandemic. The individual impact of impairment can be high – ranging from nutritional disturbances, to social dysfunction and insidious mental ill health [2–6]. These effects are particularly pronounced in qualitative disorders such as parosmia [7–9] – the pathophysiology of which remains largely unknown. Moreover, new evidence continues to link olfactory dysfunction with major health outcomes such as neurodegeneration and death [10–12].

In an effort to promote quality of clinical care and guide new research, we provide the following review of current literature and expert agreed recommendations on the assessment and management of olfactory dysfunction.

Materials and methods

Current olfactory literature was systematically reviewed for each respective topic from December 2021 to February 2022. Databases interrogated included Medline (via PubMed, inception - current), Embase (Jan 1958 – current), Cochrane Central Register of Controlled Trials (CENTRAL) (inception – current), and Google Scholar (only first 1,000 results were reviewed). MedRxiv and BioRxiv were also screened for relevant preprints. Search terms were devised using appropriate truncation, Boolean operators (within and between domain), and MeSH term mapping where relevant. Finally, citing literature and reference lists for included studies were hand-searched.

Expert agreement for the included recommendations was assessed using a modified Delphi process (RAND/UCLA methodology) [13]. Recommendations were devised by KLW and TH and distributed to a subgroup of co-authors for initial content review. Further discussion was then undertaken by a steering group comprising members of the Clinical Olfactory Working Group, prior to formal scoring, The manuscript and recommendations were then distributed to all co-authors, who were asked to score their agreement with the recommendations on a Likert scale (1-9: 1 being the lowest and 9 being the highest level of agreement). Results were classified as: agreed (≥70% score 7-9, ≤15% score 1-3), disagreed (≥70% score 1-3, ≤15% score 7-9) or no consensus. Full agreement on all recommendations was achieved during the first Delphi round. Further rounds were therefore not undertaken.

Terminology

Olfactory dysfunction (OD) can be classified as either quantitative, involving alteration in the strength but not quality of odours, or qualitative, in which the quality of odours is changed or there is perception of smell in the absence of an odour stimulus. Qualitative disorders, such as parosmia, often involve negatively perceived changes in quality of smell. Very often, qualitative changes are found in combination with quantitative changes, whereas it is much less frequent to find qualitative changes alone. With regard to qualitative changes, parosmia and phantosmia often occur together, but may also appear separately. Definitions of terms used to describe olfactory function and dysfunction are listed in Table 1.

There has previously been disagreement in the literature regarding terminology. Whilst 'parosmia' is generally used to indicate a qualitative olfactory distortion in the presence of a stimulus, it has on occasion been used to describe more general OD (including quantitative loss) [14]. 'Dysosmia' has been used by some to describe any distortion in olfaction, which would therefore include both quantitative and qualitative changes [14,15]. However, others have used this term with reference to qualitative dysfunction in the presence of an odourant stimulus only, thus making it synonymous with parosmia [16]. Whilst the term 'cacosmia' is generally accepted as a 'negatively perceived olfactory perception', often in the presence of an endogenous odour source (e.g. from the sinuses), some consider this either a form of parosmia (stimulus present) [16], phantosmia (stimulus absent) [14], or both [15]. Euosmia is used to describe qualitative olfactory distortion in the presence of a stimulus that is typically considered as pleasant and can therefore be considered a subtype of parosmia [17]. Troposmia is generally considered to be synonymous with parosmia [14], but has not been used often. Olfactory agnosia has been mentioned as an inability to recognize odors. In light of these inconsistencies, clear definitions of olfactory terms have recently been proposed (Hernandez et al., [208]), which are in line with those found in Table 1. Of note, the term 'functional anosmia' has been replaced by 'anosmia', with the same corresponding definition: quantitatively reduced olfaction to the extent that the subject has no function that is useful in daily life.

Care should be taken when using the words 'taste' and 'flavour' – particularly when discussing with patients or other lay audiences. Whilst 'taste' should only be used to describe gustation, 'flavour' describes the perception during eating and drinking, that involves gustation, retronasal olfaction, chemesthetic and food-texture related sensations.

It should be noted that hyperosmia is extremely rarely reported (though it has been so, for example, in association with migraine [18]) and its existence as an organic olfactory disorder is debated. Multiple chemical sensitivity (MCS; also known as 'Idiopathic Environmental Intolerance') is a condition in which patients describe a range of subjective symptoms following exposure to various chemicals. Due to the range of organ systems affected and disparity of offending substances, it has also been suggested that MCS is not an organic clinical entity, but rather a predominantly psychological condition. This view has been supported by studies demonstrating no significant difference in patient response to 'active' substances versus placebo [19,20]. For this reason, MCS has not been considered further in this position paper, but we would refer to the recent review by Zucco and Doty [21].

Finally, specific anosmia is thought to be a normal physiological trait with little or no clinical significance [22].

Recommendation:

➢ We recommend the use of the terms highlighted in bold in the above table, with their associated definitions.

o Delphi results: Agreed (score 7-9 = 100%, average score 8.7).

Epidemiology of olfactory dysfunction

The prevalence of OD in the general population has been dynamically evolving since the onset of the COVID-19 pandemic. In both COVID-19-associated and non-COVID-19-associated OD, epidemiological estimates vary widely according to sample demographics, definitions of impairment, and assessment technique. The following sections will discuss epidemiological evidence for the prevalence of non-COVID-19-associated OD. For a discussion of prevalence in COVID-19-associated OD, please see section on 'Causes and Classification of Olfactory Loss', subsection 'COVID-19-associated Olfactory Dysfunction'. Furthermore, unless otherwise stated, the following estimates are for quantitative OD. For a discussion of prevalence in qualitative OD, please see section on 'Qualitative Olfactory Dysfunction'.

Studies using only subjective reporting

Population based studies using subjective methods of assessment have produced estimates ranging from 1.4 to 23% (see Table 2). This variance appears to depend on the precise nature of the question asked, in addition to potential demographic and true population level differences. For example, two studies analysing the prevalence of self-reported olfactory impairment have been published using data from the US-based National Health and Nutrition Examination Survey (NHANES). Analysing 2011-2012 data, Bhattacharyya and Kepnes [23] estimated that 10.6% ± 1.0% of the US population had experienced smell disturbance in the last 12 months. In 2016, Rawal and colleagues also published results from the 2011-2012 NHANES data [24]. They reported a higher prevalence of subjective OD at 23%. However, in this case, impairment was defined 'since age 25'. Also of interest, Huang and colleagues [25] assessed subjective olfactory function in China using a single question that was modelled on the earlier US-based 'Disability Supplement to the National Health Interview Survey' [26]. The prevalence of OD demonstrated in China was similar to that found in the USA, at 2.4 and 1.4% respectively. True population prevalence notwithstanding, the similarity of these estimates may be influenced by the similarity of the question construct. With this in mind, care should be taken when generalising the results of studies using subjective assessment alone.

Studies including psychophysical testing

In addition to the above, previous work has demonstrated poor correlation between subjective assessment and less biased 'objective' psychophysical tests of olfaction (for full discussion, please see section on 'Clinical Assessment', subsection 'Olfactory Testing'). Indeed, epidemiological work has demonstrated either no correlation between subjective and psychophysical measures [27], or very low levels of self-reporting sensitivity [28]. Therefore, recent epidemiological studies have moved towards the use of psychophysical assessment in place of, or often in addition to, subjective patient reporting.

Prevalence estimates based on psychophysical assessment have been produced from a number of countries internationally, including Germany, Sweden, Spain, Mexico, the USA, Australia and Taiwan. The majority of studies report odour identification scores, though some have used composite 'TDI' (threshold, discrimination and identification – see section on 'Clinical Assessment') scores, or, for example, separate detection, recognition and identification scores. In general, prevalence estimates produced using psychophysical tools are higher than those using subjective assessment (Table 2 and 'meta-analysis' section below). Again, however, when comparing such estimates, the exact nature of the psychophysical tool as well as the definition of OD used should be noted.

Olfactory function deteriorates with age. This has been demonstrated by a number of geographically disparate studies (see Table 2), some of which have estimated OD to affect more than 50% of older adults [29–34]. Comparing subjective with psychophysical outcomes, the ability to self-assess olfactory function also appears to decrease with age (27,34). Indeed, the sensitivity of self-report can be as low as 35% in people over 60 years of age (28). Furthermore, epidemiological studies have helped to establish the link between OD and impaired cognitive health. For example, an early study from Graves and colleagues demonstrated an increased risk of cognitive decline in older adults with idiopathic OD and one or more APOE-ε4 alleles. They also found that the 12-item Cross-Cultural Smell Identification Test (CC-SIT) classified people with cognitive decline more accurately than global cognitive testing [29]. More recently, Schlosser and colleagues demonstrated a significant association between a composite olfactory test score ('TDI' score), as well as an odour discrimination score, and cognitive function as determined using the Mini-Mental State Examination [35].

Olfaction additionally appears to correlate with general health in the aging person [36], meaning it could be used as an early biomarker for age-related decline. In their study of Australian older adults, Karpa et al., demonstrated a negative correlation between odour identification scores and body mass index [37] – a finding which could reflect an overlap between age-related OD,

anorexia and frailty. Further analysis of this data from Gopinath and colleagues in 2012 demonstrated decreased independence (as measured by increased dependence on community and informal support services and difficulty in performing activities of daily living) in older adults with OD, after controlling for confounding factors such as cognitive function [38]. In another study by Van Regemorter and colleagues, OD was found to predict frailty and poor postoperative outcome in older patients scheduled for elective non-cardiac surgery [39]. Gopinath and colleagues also demonstrated an increased risk of all-cause 5-year mortality in older adults with moderately impaired olfaction, compared with those with normal olfaction (multivariable-adjusted hazard ratio 1.68, 95% CI 1.10—2.56) [40]. The link between OD and increased risk of mortality has also been shown in other studies. Devanand and colleagues reported a statistically significant, independent association between OD (particularly anosmia) and increased risk of mortality, in North American older adults [41]. Logistic regression of data from another US-based study of older adult (National Social Life, Health, and Aging Project (NSHAP)) further demonstrated OD to be an independent predictor of 5-year mortality [10,11,42].

OD has also been linked to other factors, such as male sex [43], smoking [44] and race/ethnicity [43,45], in some, but not all studies. With regards to the latter, data from the NSHAP study demonstrated significant racial disparity – with African Americans and Hispanic Americans being more likely to have age-related olfactory loss (presbyosmia) than White Americans, after controlling for age and gender [45]. Cognition, education, and household assets were found to account for differences between White Americans and Hispanic Americans, but neither these nor other potential confounding factors could account for the comparative impairment in African Americans.

Meta-analysis

A recent meta-analysis pooled data from 25 studies, to include a total of 175,073 participants (mean age 63 years, 56.3% male) [46]. The overall prevalence of OD was 22.2% (95% CI 14.8 - 30.6%). Prevalence of OD was significantly higher when psychophysical tools were used, as opposed to subjective patient report (28.8% and 9.5% respectively, $p<0.001$) and was also greater where psychophysical tools employed more than 8 odour stimuli (30.3% vs 21.1%). As has been demonstrated extensively already, this meta-analysis confirmed that prevalence of OD increases with age.

Key Points:

- ➢ Estimates of olfactory dysfunction prevalence vary with assessment method and should ideally be determined using a validated psychophysical tool for the population in question, in addition to subjective reporting.
- ➢ Meta-analytic work demonstrates that olfactory dysfunction affects approximately 22% of the general population.
- ➢ Normal aging significantly contributes to this burden.

Table 2. Epidemiological studies addressing olfactory dysfunction.

Author/s	Study	Sample Population	Location	Assessment Tool	Prevalence Estimates	Other
Desiato et al., 2021 [46]		175,073, aged 18-101 years	Europe, USA, Australia, Asia	Subjective and Psychophysical (Brief and Expanded Identification Tests, Sniffin' Sticks/ Butanol Threshold Test)	OD: 22.2% overall prevalence; 28.8% psychophysical; 9.5% subjective	Prevalence of OD was greater where psychophysical tools used more than 8 odour stimuli; prevalence increases with age
Castillo-López et al., 2020 [673]	Olfaction in Mexico (OLFAMEX)	1,921, aged 16-59 years	Mexico	Subjective and Psychophysical (OLFAMEX-4)	Anosmia: 0.1% detection, 0.5% recognition, 1.8% identification; Hyposmia: 7.1% detection, 20.9% recognition, 53.8% identification	Deterioration of odour detection, recognition, and identification in participants ≥40 years
Schlosser et al., 2020 [35]		176, aged 20-93 years	USA	Psychophysical ("Sniffin' Sticks", odour threshold, discrimination, and identification test)	OD: 53.4% overall; 5.7% anosmia; 47.7% hyposmia	Significant associations between the following: TDI score and MMSE score; threshold score and age; discrimination score, age and MMSE score; identification score and age
Hinz et al., 2019 [31]	Leipzig Center for Civilization Diseases (LIFE)-Adult-Study	7,267, aged 18-80 years	Germany	Psychophysical ("Sniffin' Sticks" 12-item odour identification test)	5.1% anosmia; 52.4% hyposmia; 42.5% normosmia	No association between olfactory function and QoL
Huang et al., 2017 [25]	Kailuan study	12,627 adults aged 25-95 years	China	Subjective (based on NHIS questionnaire)	2.4% smell dysfunction	Worse smell and taste dysfunction was associated with higher total cholesterol concentrations
Seubert et al., 2017 [28]	Swedish National Study on Aging and Care in Kungsholmen (SNAC-K)	2,234, aged 60-90 years	Sweden	Subjective and Psychophysical ("Sniffin Sticks" 16-item Odour Identification Test)	OD: 24.8% ("Sniffin' Sticks"), 17 % (Subjective)	Self-report had poor sensitivity (31%), but good specificity (87%)
Hirsch et al., 2016 [674]	Chronic Rhinosinusitis Integrative Studies Program (CRISP)	7,847, aged 39-71 years	USA	Subjective (part of CRS prevalence study)	9.4% smell loss	
Hwang et al., 2016 [675]	Korea National Health and Nutrition Examination Survey (KNHANES)	11,609, aged ≥ 19 years	Korea	Subjective	6.3% with OD	Prevalence of OD was higher in older people with metabolic syndrome than those without
Liu et al, 2016 [43]	National Health and Nutrition Examination Survey (NHANES)	3,519, aged ≥40 years	USA	Psychophysical (NHANES Pocket Smell Test)	13.5% smell impairment only; 2.2% smell and taste impairment	Higher rates of OD in older age, men, and ethnic minorities
Rawal et al., 2016 [24]	National Health and Nutrition Examination Survey (NHANES)	3,603, aged ≥ 40 years	USA	Subjective (Chemosensory Questionnaire (CSQ))	16.7% smell loss since age 25; 23% any smell alteration; 6% phantosmia; highest prevalence of smell alteration in ≥ 80 years (32%)	
Bhattacharyya & Kepnes, 2015 [23]	National Health and Nutrition Examination Survey (NHANES)	3,594 adults, aged ≥ 40 years	USA	Subjective (last 12 months)	10.6% with smell disturbance in the last 12 months [of these, 50.2% ± 1.8% reported their problem was 'always there'; 45.2% ± 2.2% 'comes and goes'; and 4.5% ± 0.9% 'only present with a cold']	Prevalence increased with age, but was not affected by sex

Author/s	Study	Sample Population	Location	Assessment Tool	Prevalence Estimates	Other
Devanand et al., 2015 [41]	Washington Heights / Inwood Columbia Aging Project	1,169, aged ≥65 years	USA	Psychophysical (SIT-40)	Average score was 25.18 ± 7.26 (between "severe microsmia" and "microsmia")	Lower SIT-40 score was found to be statistically significantly and independently associated with an increased risk of mortality
Kern et al., 2014 [676]	National Social Life, Health, and Aging Project (NSHAP)	2,094, aged 62-90 years	USA	Psychophysical (Olfactory Function Field Exam (OFFE, odour identification and detection)		Detection and identification ability was worse at older ages
Pinto et al., 2014a [45]	National Social Life, Health, and Aging Project (NSHAP)	3,005, aged 57-85 years	USA	Psychophysical (Olfactory Function Field Exam (OFFE, odour identification and detection)	1.1% were unable to identify any odour (anosmia or severe hyposmia)	African Americans and Hispanics were more likely to have presbyosmia than white Americans
Lee et al., 2013 [677]	Korea National Health and Nutrition Examination Survey (KNHANES)	7,306, aged 20-95 years	Korea	Subjective	4.5% with OD	Increasing prevalence with age
Gopinath et al., 2012a [38]	Blue Mountains Eye Study	1,636, aged ≥60 years	Australia	Psychophysical (San Diego Odour Identification Test (SDOIT)		Decreased independence in older adults with OD
Gopinath et al., 2012b [40]	Blue Mountains Eye Study	1,636, aged ≥60 years	Australia	Psychophysical (San Diego Odour Identification Test (SDOIT)		Moderate olfactory loss was associated with a 68% increased risk of all-cause mortality
Mullol et al., 2012 [285]	Olfaction in Catalonia (OLFACAT)	9,348, aged 5-91 years	Spain	Psychophysical (4 self-administered microencapsulated odourants)	Overall prevalence of OD: 19.4% detection, 43.5% recognition, 48.8% identification; Anosmia: 0.3% detection, 0.2% recognition, 0.8% identification; Hyposmia: 19.1% detection; 43.3% recognition; 48% identification	Significant and progressive age-related decline of smell detection, smell recognition and identification increased up to the 4th decade of life, plateaued up to the 6th decade and declined after
Schubert et al., 2012 [678]	Beaver Dam Offspring Study (BOSS)	2,838, aged 21-84 years	USA	Subjective and Psychophysical (San Diego Odour Identification Test (SDOIT))	OD: 3.8% mean prevalence for adults (rising to 13.9% for adults ≥65 years, SDOIT)	Prevalence of OD was greater among men and older age groups
Boesveldt et al., 2011 [679]	National Social Life, Health, and Aging Project (NSHAP)	3,005, aged 57-85 years	USA	Psychophysical (5-item "Sniffin' Sticks" odour identification test)	Severe OD in 2.7%	
Hastan et al., 2011 [209]	Global Allergy and Asthma European Network (GA2LEN)	57,128, aged 31-58 years	Europe	Subjective (part of CRS prevalence study)	OD: 7.6% of total sample; 48.5% of patients with CRS based on EPOS criteria	
Karpa et al., 2010 [37]	Blue Mountains Eye Study	1,636, aged ≥60 years	Australia	Psychophysical (San Diego Odour Identification Test (SDOIT)	27% olfactory impairment	Prevalence of OD increased two-fold with each decade of life after 60 years and was higher in men
Lin et al., 2009 [294]		211, aged 19-89 years	Taiwan	Subjective and Psychophysical ("Sniffin' Sticks" 16-item odour identification test)	12.3% olfactory dysfunction; 10% parosmia; 30.8% phantosmia	

Author/s	Study	Sample Population	Location	Assessment Tool	Prevalence Estimates	Other
Shu et al., 2009 [27]		1,005, aged 18-89 years	Taiwan	Psychophysical (Modified "Sniffin' Sticks" 16-item odour identification test)	Measured OD: 3.7% (18-35 years), 17.4% (36-55 years), 35.6% (>55 years); Subjective OD: 9% (18-35 years), 14% (36-55 years), 12% (>55 years)	No significant correlation between subjective and measured OD
Ross et al., 2008 [32]	Honolulu-Asia Aging Study (HAAS)	2,267 men, aged 71-95 years	USA	Psychophysical (12-item Cross-Cultural Smell Identification Test (CC-SIT))	Impaired odour identification in ~3/4 of adult men ≥71 years	
Vennemann et al., 2008 [44]	Dortmund Health Study (DHS)	1,277, aged 25-75 years	Germany	Psychophysical ("Sniffin' Sticks" 12-item odour identification test)	22.1% impaired olfaction; 3.8% anosmia; 18.3% hyposmia	Prevalence increased with age and cigarette smoking
Nordin et al., 2007 [293]	Skövde Population-Based Study	1713, aged ≥20 years	Sweden	Subjective (structured interview for adults, questionnaire for teenagers)	3.9% overall prevalence of parosmia (4% in adults, 3.4% in teenagers)	Significant difference in parosmia prevalence across age groups
Wilson et al., 2006 [33]	Memory and Aging Project (MAP)	481, aged 74-88 years	USA	Psychophysical (12-item Cross-Cultural Smell Identification Test (CC-SIT))	Impaired odour identification in 55.3%	
Brämerson et al., 2004 [680]	Skövde Population-Based Study	1,387, aged ≥20 years	Sweden	Psychophysical (Scandinavian Odour Identification Test (SOIT))	19.1% overall prevalence; 5.8% anosmia; 13.3% hyposmia	
Landis et al., 2004 [326]		1,240, aged 5-86 years	Germany	Subjective and Psychophysical ("Sniffin' Sticks" 16-item odour identification test)	4.7% anosmia; 16% hyposmia; 2.1% parosmia, 0.8% phantosmia	
Larsson et al., 2004 [681]	Betula Project	1,906, aged 45-90 years	Sweden	Psychophysical (Modified Scandinavian Odour Identification Test (SOIT))		Age-related deterioration in odour identification performance
Nordin et al., 2004 [682]	Skövde Population-Based Study	1,387, aged ≥20 years	Sweden	Subjective (self-report: poorer than normal, normal, better than normal)	15.3% "poorer-than-normal" olfactory function	Significant difference in prevalence of "poorer-than-normal" olfactory function across age groups
Murphy et al., 2002 [34]	Epidemiology of Hearing Loss Study	2,491, aged 53-97 years	USA	Subjective and Psychophysical (San Diego Odour Identification Test (SDOIT))	OD: 24.5% mean prevalence for adults, rising to 62.5% for adults over 80 years (SDOIT); 9.5% (self-report)	Prevalence of OD was greater among men and older age groups
Graves et al., 1999 [29]	Community-based longitudinal study of memory and aging in the Japanese-American community in King County, Washington	1,604, aged ≥65 years	USA	Psychophysical (12-item Cross-Cultural Smell Identification Test (CC-SIT))	OD: 56.9% overall; 10.5% anosmia; 46.4% microsmia	CC-SIT more accurately classified people with cognitive decline compared to global cognitive testing
Hoffmann et al., 1998 [26]	Disability Supplement to the National Health Interview Survey (NHIS)	80,000, randomly selected adults (>18 years)	USA	Subjective (impaired smell lasting >3 months)	1.4% with an olfactory problem; rising to 40% with a chemosensory problem ≥ 65 years	Exponentially increasing prevalence with age

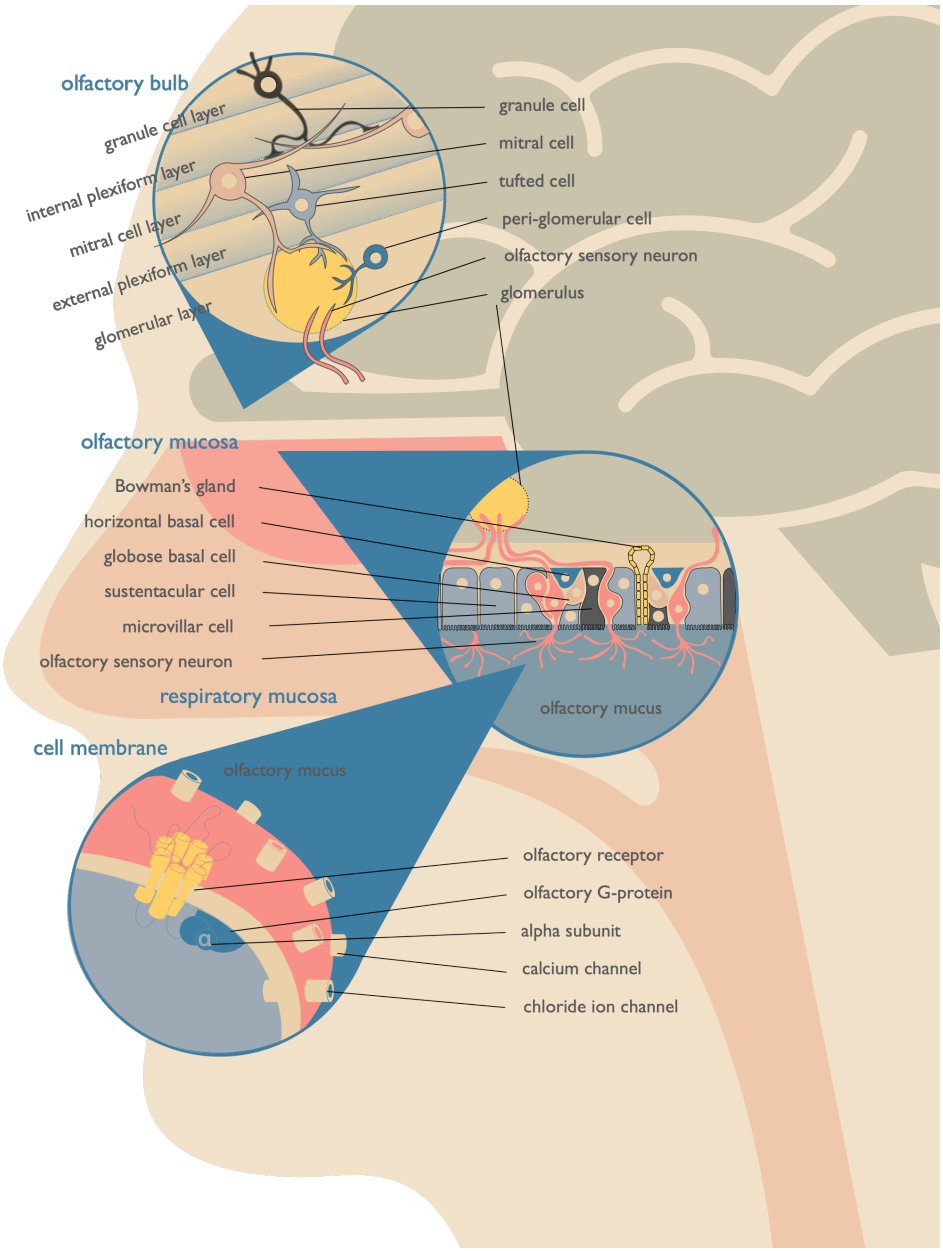

Figure 1. Anatomy of the olfactory bulb, olfactory mucosa, and cell membrane.

ANATOMY AND PHYSIOLOGY OF OLFACTION

Except in rare circumstances in which intact olfactory function can be demonstrated in people without radiologically apparent olfactory bulbs [47], the perception of smell requires a functional peripheral sensory organ and central pathways.

Approximately 6-30 million olfactory sensory neurons (OSN), can be found in the olfactory neuroepithelium (OE) of young adult humans, whose axons collectively constitute the olfactory nerve (cranial nerve 1) [48]. The cell bodies of these bipolar neurons are found within the OE, a pseudostratified columnar epithelium which contains three main cell types: OSNs, basal cells (a stem cell population including horizontal and globose subtypes) and supporting (sustentacular) cells (for more details regarding the latter cell type, see: COVID-19-associated post-infectious olfactory dysfunction). Under both homeostatic conditions and following injury, OSN undergo replacement by the resident stem cell population. Therefore, the OSN present within the OE are at various stages of maturation. The OE is separated from the underlying lamina propria (which contains Bowman's glands, vascular networks, connective tissue, olfactory ensheathing cells and olfactory nerve fibroblasts) by a basal membrane and collectively these structures (OE, basal membrane and lamina propria) make up the olfactory mucosa. Overlying the OE is a thin layer of olfactory mucus, which is secreted from Bowman's glands, and likely mixes with goblet cell output from neighbouring respiratory mucosa. Odourants must enter into the mucus layer prior to binding with olfactory receptors (OR) found on the dendrites of OSN, a process which is facilitated by odorant binding proteins (OBP). Apically, mature OSNs extend multiple dendritic cilia into the olfactory mucus layer, creating a large surface area for odourant binding [49].

Olfactory receptors are G protein-coupled receptors and binding of an odourant ligand leads to downstream signalling cascades involving activation of adenylyl cyclase and subsequent opening of cAMP-dependent cation channels (50). Resultant action potential generation is then propagated along the axons of OSNs towards the olfactory bulb (OB) and central olfactory networks. A mature OSN is thought to express only one intact odorant receptor (OR) gene [50] out of a repertoire of approximately 400 active genes [51]. Despite this, humans are able to detect thousands of distinct odours [52–54]. This is made possible through complex combinatorial encoding, whereby each odourant ligand is recognised by varying combinations of OR, where they can act as agonists and antagonists [55–58]. In addition, other types of chemoreceptors have been identified which are likely to be involved in human chemoreception [59–61].

Traditionally thought to be limited to the olfactory cleft (OC), there is uncertainty about the extent of the OE within the human nasal cavity [62]. Recent work has demonstrated proportionally similar distribution in the embryonic and adult nasal cavities, though there also appears to be a reduction in OE area with age, progressing from an anterior-ventral to a posterior-dorsal direction [63]. Some studies have found mature and functional OSN at the insertion of the middle turbinate [64–68], whilst others have not [63].

Basally, each mature OSN projects a single axon through the basal membrane into the lamina propria, where it is received by olfactory ensheathing cells (specialized glial cells which are also found in the OB) [639, 718, 719]. Progressively, OSNs and olfactory ensheathing cells together form olfactory axon fascicles of increasing diameter which become enwrapped by perineurial olfactory nerve fibroblasts [720-725]. Those bundles (olfactory fila) run- through the foramina of the cribriform plate towards the OB. The OB is the first relay in the olfactory system and is found immediately superior (dorsal) to the cribriform plate and inferior (ventral) to the orbitofrontal cortex. Within the OB, OSN axons form their first synapse with bulbar glomerular cells. It is therefore interesting that OSNs are first order excitatory sensory neurons, which extend directly from the mucosa of the OC into the brain. In this way, they are exposed to the external environment, including pathogens and toxins that can cause damage and/or death. OSN neurogenesis, which, under healthy circumstances occurs during adulthood, may be a compensatory response to such exposure and associated damage [69,70].

The second order output neurons from the olfactory bulb are the mitral and tufted cells. Following signal integration, these neurons extend their axons along the lateral olfactory tract towards the structures of the primary olfactory cortex. These structures include: the anterior olfactory nucleus, the piriform cortex, the periamygdaloid cortex, the anterior cortical nucleus of the amygdala and the rostral entorhinal cortex. Odour processing also involves 'secondary' and 'tertiary' brain areas, including structures such as the hippocampus, parahippocampus, insula, and orbitofrontal cortex [71–73].

Finally, it is important to remember that the sensation of smell is also influenced by the somatosensory and chemesthetic sensations of the nose: for example, the cooling sensation of menthol

or the prickle of carbon dioxide from carbonated drinks. These sensations are mediated in the nose by the trigeminal nerve [74,75], and there is increasing evidence that trigeminal and olfactory functions are closely linked and potentially interdependent [76–79]. In addition, trigeminal activation is crucial to the perception of nasal airflow [80–83]. In addition to trigeminal nerve effects, gustation has also been reported to enhance olfactory sensation (i.e., sweet tastants enhancing the perceived sweetness of odors) [84].

Key point:

➢ Olfactory sensory neurons are prone to damage due to their exposed position, but are capable of regeneration from stem cells found within the olfactory neuroepithelium.

Table 3. Definition of olfactory dysfunction according to anatomical location of lesion.

Conductive dysfunction	Resulting from blockage of odourant transmission to the olfactory neuroepithelium.
Sensorineural dysfunction	Resulting from damage/loss of the olfactory neuroepithelium or nerve.
Central dysfunction	Resulting from damage/loss of the olfactory processing pathways of the central nervous system.

Causes and classification of olfactory dysfunction

Previous attempts have been made to classify OD according to the location of presumed pathology, in a similar way to classification used in the auditory system. In this way, definitions have included those as in Table 3.

However, anatomical classification in this way may be restrictive. The above categories are not mutually exclusive and their use as such may lead to incomplete appreciation of the underlying pathophysiology. This is particularly evident with regards to several conditions known to cause OD.

Chronic rhinosinusitis (CRS) is a common inflammatory condition affecting the mucosa of the nose and one or more of the paranasal sinuses [85]. It has several distinct phenotypic subtypes including CRS with or without polyps. It has been suggested that hyposmia and anosmia associated with CRS is caused by mechanical obstruction of odourant transmission to the OC due to mucosal oedema or polyps [86]. Accordingly, opacification of the OC on CT has been correlated with olfactory function [87]. Alone, this would make CRS a conductive OD. However, the link between eosinophilia and OD has been well demonstrated [88–92], and increasing evidence from both animal models and human research has suggested that inflammation within the neuroepithelium can lead to temporary, reversible interference with odourant binding/olfactory perception [93,94]. Furthermore, long-term inflammation is believed to cause shifts in olfactory stem cell populations from regenerative to immune phenotypes [95], neuroepithelial remodelling and replacement with respiratory type epithelium [96,97]. Olfactory bulb volumes are additionally decreased in patients with CRS [98]. Indeed, Gudziol and colleagues have shown that olfactory bulb volume can increase significantly after treatment in patients with CRS, compared with controls [99]. Finally, reduced grey matter volume has been demonstrated despite preserved OB volume in patients with CRS [100], and olfactory eloquent areas have been shown to undergo both functional and structural plasticity after surgical treatment for CRS [101,102]. Therefore, it would appear that OD due to CRS may be a combination of conductive, sensorineural, and even central components in established disease. These observations make an argument against the anatomical classification of olfactory disorders.

Similar anatomical overlap might be described in post-traumatic olfactory dysfunction (PTOD). The causative pathology in these cases has traditionally been described as severing of the olfactory nerve filaments as they cross the cribriform plate to reach olfactory bulb [103]. However, the temporal course in such patients often does not fit with such dramatic and complete damage, but rather with delayed central damage, for example, through cortical oedema [104]. In addition, the degree of PTOD can be correlated with central lesions, demonstrated with magnetic resonance imaging (MRI) of the brain [104]. In this way, the anatomical site of the lesion might either be sensorineural, central, or both. One should also bear in mind that facial lesions obtained during head injury may cause obstruction of airflow to the OC, thereby contributing a conductive element to any OD.

To bypass these limitations in classification, chemosensory research has evolved to describe OD according to putative underlying aetiology. Whilst an extensive number of underlying aetiological conditions have been linked to OD, the main causes are as follows:

- Post infectious olfactory dysfunction (PIOD)
  - o COVID-19-associated PIOD (C19OD)
  - o Non-COVID-19-associated PIOD
- Olfactory dysfunction secondary to sinonasal disease
- Post-traumatic olfactory dysfunction (PTOD)
- Olfactory dysfunction associated with neurological disease
- Olfactory dysfunction associated with exposure to drugs/toxins
- Congenital olfactory dysfunction
- Olfactory dysfunction associated with aging (presbyosmia)
- Other possible causes: iatrogenic - complications (e.g., sinonasal and skull base surgery), iatrogenic - consequence (e.g., laryngectomy), tumours, multiple systemic co-morbidities
- Idiopathic olfactory dysfunction

The following sections will describe the clinical presentation and current pathophysiological evidence for the above classifications, with an emphasis on COVID-19-associated OD (C19OD) which is discussed separately to other causes of PIOD, given the large amount of expressly SARS-CoV-2 focused research produced since the start of the pandemic.

Qualitative OD (including parosmia and phantosmia) may be related to a number of underlying aetiologies and will therefore be discussed in depth separately in the section on "Qualitative Olfactory Dysfunction'.

COVID-19-associated post-infectious olfactory dysfunction

Prevalence and clinical presentation

Following extensive media coverage and geographically disparate anecdotal reports, OD was officially recognised by the World Health Organisation as a symptom of COVID-19 in May 2020. Concurrent to this, research began to delineate the clinical presentation, course and prevalence of C19OD.

Prevalence estimates are, as for epidemiological work, dependent on the method of assessment. Subjective patient report formed the basis for many early estimates, given the inherent difficulty in psychophysically assessing patients who were acutely infectious. A meta-analysis of 3,563 patients performed early in the pandemic demonstrated an overall prevalence of 47%, which rose to 67% in those who were mild to moderately symptomatic [105,106]. Methods of assessment used in the included studies ranged from review of medical records and ad hoc questions to validated patient-reported outcome measures (PROMs) such as the Sino-nasal Outcome Test (SNOT-22) and the Short version of Questionnaire of Olfactory Disorders - Negative Statements (sQOD-NS) [107,108]. In a large online survey that collected visual analogue scale (VAS)-based information on chemosensory dysfunction in 4,039 COVID-positive patients from 41 countries, mean difference scores (pre- vs mid-/post- infection) in smell, taste and chemesthesis were -79.7 ± 28.7 (mean ± SD), -69.0 ± 32.6, and -37.3 ± 36.2, respectively [109]. Using an updated sample of this data, patients with confirmed COVID-19 were compared with those with non-COVID-19 respiratory illness. The authors demonstrated that subjective smell loss was the best predictor of COVID-19 in patients experiencing respiratory symptoms – specifically, VAS smell ratings were more predictive than binary yes/no questions covering chemosensation or other cardinal symptoms such as fever or cough [110]. In another study addressing the predictive value of OD in COVID-19, Haehner and colleagues found that subjectively reported 'sudden smell loss' had a specificity of 97%, sensitivity of 65%, a positive predictive value of 63% and a negative predictive value of 97% (where patients with nasal congestion were excluded) [111]. Perhaps the largest cohort of subjective data was provided through a UK/USA app-based symptom tracker [112]. In 18,401 respondents who had undergone SARS-CoV-2 testing, subjective loss of smell/taste was more common in those with a positive test result (65.03% of 7,178 people) than those with a negative result (21.71% of 11,223 people) (odds ratio = 6.74; 95% confidence interval = 6.31–7.21).

The estimated prevalence of C19OD is higher where psychophysical tools are used. A systematic review and meta-analysis by Hannum and colleagues demonstrated pooled prevalence estimates of 77% (95% CI of 61.4–89.2%) and 44% (95% CI of 32.2–57.0%) where psychophysical and subjective measurements were employed, respectively [113]. Using the "Sniffin' Sticks", Huart and colleagues found that composite TDI, as well as individual identification and discrimination test scores discriminated between patients with COVID-19, and those with acute colds [114]. Where a cut off value of ≤10 was taken, identification discriminated with a sensitivity of 100% and specificity of 80%. In light of these differences, self-administered psychophysical tests have been proposed, which will be discussed in more detail in the section on 'Clinical Assessment', subsection 'Olfactory Testing - Psychophysical Testing.'

In some patients, OD is the only symptom of COVID-19 infection [115–117]. In others, the onset of C19OD either precedes or is concurrent with the onset of other symptoms. Borsetto and colleagues found this to be the case in 20% and 28% of patients, respectively [105]. During early waves of the pandemic, many patients reported C19OD in the absence of rhinitic symptoms such as rhinorrhoea and nasal congestion [110,114,118]. However, with later variants such as omicron and its derivatives, rhinitic symptoms are more commonly reported, often with a reduction in the proportion of patients reporting OD. For example, C19OD was only reported in 1 in 5 users of the UK-based COVID Symptom Study ('Zoe') App during a period in which omicron was thought to be the dominant strain (December 2021)[119]. Indeed, based on subjective reporting, Boscolo-Rizzo and colleagues demonstrated reduced prevalence of OD in association with infection during the omicron-dominant period, compared with the initial wave of infection at the start of the pandemic [120]. Similar results were demonstrated by the REal-time Assessment of Community Transmission (REACT-1) study, which reported subjective symptoms from 1,542,510 randomly selected participants in England from 1.5.20 to 31.3.22 [121]. A recent systematic review and meta-analysis of OD in patients infected with the omicron variant demonstrated a global prevalence of 3.7% [122]. However, this varied geographically, with higher rates seen in people of European ancestry (11.7%). This variation is thought to reflect geographical differences in polymorphisms of the UGT2A1/UGT2A2 locus (which encodes an odorant-metabolising enzyme, UDP glycosyltransferase)[123].

With regards to sex and age distribution, some studies have documented OD more frequently in younger patients and in women than men [124,125]. In the aforementioned online survey of 4,039 COVID-positive respondents, 72% were female. However, care should be taken when interpreting such results in light of possible selection bias related to gender differences in healthcare seeking and reporting behaviour.

In early studies relying on subjective patient reporting, the mean duration of C19OD was found to be approximately 10 days [126,127], with recovery rates of between 32 to 89% [128–130].

However, studies using psychophysical testing have demonstrated slower recovery, and higher proportions of patients with PIOD. Using "Sniffin' Sticks", Prem and colleagues tested 102 patients between 111-457 days (mean of 216 days) after onset of C19OD [131]. They found a group mean TDI score of 27.1 (SD 5.8; range 4.3–38.5): 4.0% were anosmic, 72.5% hyposmic, and the remainder were normosmic. A case control study investigating the prevalence of OD in 340 people (170 cases/170 controls), demonstrated a significantly higher prevalence of OD in COVID-19 cases than non-COVID-19 controls (26.5% of cases (21.8% hyposmia, 4.7% anosmia) and 3.5% of controls) [132]. Using "Sniffin' Sticks" (full TDI-score) Tognetti and colleagues demonstrated persistent OD in 37% of 98 patients tested at 18 months, of whom 33% were hyposmic and 4% were anosmic [133]. Sixty percent of these patients were unaware of their persistent dysfunction. Longer follow up is available using subjective assessment – with studies producing a wide range of recovery rates at two years: McWilliams et al., reported full recovery in only 38.2% of 267 respondents [134], whilst Boscolo-Rizzo et al., demonstrated subjective recovery in 88.2% of respondents [135]. Recent meta-analytic work including studies with both subjective and objective chemosensory outcomes projected persistent PIOD in 5.6% of patients [136]. Another recent systematic review and meta-analysis demonstrated a higher prevalence - with persistent OD in approximately 30% of patients, 6 months after initial infection [137]. Extrapolating from these figures, the future burden of COVID-19-associated PIOD could be highly significant [138].

Finally, the nature of OD in COVID-19 was initially thought to be mainly quantitative – that is, most patients reported hyposmia or anosmia [109]. However, it has become increasingly apparent that qualitative dysfunction, particularly parosmia, is highly prevalent. Parosmia may present several months after the initial onset of OD, and may appear after a period of apparent olfactory recovery [9,139]. Critically, Tognetti and colleagues found that 49% of all COVID+ patients reported parosmia at 18 months post OD onset, compared with only 5% in COVID- patients [133]. Interestingly, in COVID+ patients, only 20% of patients reporting parosmia also had quantitative OD (specifically hyposmia). This indicates that studies assessing long-term outcomes in OD should employ both formal psychophysical testing for quantitative OD, as well assessment of qualitative dysfunction. Given the significant impact of qualitative OD on quality of life [140], the pandemic has highlighted the need for increased research into the causes of and treatments for these conditions. This topic will be discussed in more detail in the section on 'Qualitative Olfactory Dysfunction'.

Pathogenesis

The pathogenesis of C19OD has not yet been fully elucidated, likely in part due to the relatively incomplete state of knowledge regarding PIOD prior to the onset of the pandemic. However, the research landscape is dynamic, with new data augmenting current hypotheses despite inherent barriers, such as infection control widely varying clinical presentations and newly emerging variants. The following section provides an overview of evidence available on the pathogenesis of C19OD at time of writing.

SARS-CoV-2 is a single stranded RNA virus with a glycoprotein spike (S protein) that binds to angiotensin-converting enzyme 2 (ACE2) on human cells, facilitated by the priming protease TMPRSS2 [141]. ACE2 has been located on the surface of cell types in various tissues, including amongst others lung, kidneys, heart, oral mucosa, and skeletal muscle. In mice, ACE2/TMPRSS2 are expressed by sustentacular cells (OSC) of the OE [142], and in vascular pericytes of the OB [143]. Non-neuronal expression by OSC, horizontal stem cells, and Bowman's gland cells has also been demonstrated in human OE [143]. Consequently, it has been widely inferred that SARS-CoV-2 causes infection of the supporting OSC population with subsequent downstream effects on olfaction. A recent human cadaveric study investigated olfactory mucosa and OB samples collected approximately one hour after death from 85 subjects, 68 of whom died of/with active COVID-19, 2 convalescent COVID-19 cases and 15 of whom served as non-COVID-19 controls [144] and identified sustentacular cells (OSC) as the target cell type in the OE for SARS-CoV-2. The authors also demonstrated evidence of viral replication within the OSC of the OE. They additionally demonstrated viral RNA within the leptomeningeal layers surrounding the OB, but none within OSN or OB parenchyma. These results suggest that acute C19OD is due to collateral effects of OE supporting cell infection, rather than direct and/or immediate neurotropism. More recent work demonstrates increased risk of C19OD with polymorphisms in the UGT2A1/UGT2A2 locus - with the resultant gene product (the odorant-metabolising enzyme, UDP glycosyltransferase) expressed by OSC [123]. Therefore, this provides further evidence that the OSC cell population is the primary site of infection.

In animals, OSC have glial as well as epithelial-like properties and undertake a variety of supportive roles, including but not limited to detoxification, phagocytosis, metabolic, secretory, absorptive, and structural support [145]. The intimate relationship between cell types is demonstrated in rats where OSC enwrap OSN dendrites [145], and in humans where OSC and adjacent OSN are connected by junctional complexes [146]. It, therefore, follows that OSC infection may lead to indirect OSN dysfunction through changes in the physiological and/or structural microenvironment. Alterations in biochemical and electrophysiological homeostasis could lead to a transient neuropraxia-type picture [147]. Following SARS-CoV-2 infection in hamsters, Zazhytska and

colleagues demonstrated transcriptional changes within OSC, and transient depletion of this cell population [148]. However, they additionally found subsequent downregulation of OR and OR signalling genes, in both hamsters and humans. This was preceded by rapid changes in nuclear OSN architecture (with dissipation of OR gene compartments) and could be precipitated by administration of UV-neutralised serum from infected animals, rather than virion itself. This suggests that changes in OSN function are caused by non-cell autonomous mechanisms, and therefore do not directly correlate with viral load. The authors further suggest that nuclear compartment disruption may either prevent reactivation of OR transcription – meaning that affected OSN would need to be replaced for restoration of olfaction – or, if it is possible for transcription to be reactivated within affected OSNs, the OR expressed may no longer match that expressed prior to infection. The former of these scenarios may lead to delayed recovery of C19OD, and the latter could potentially help to explain the frequency of COVID-19 parosmia (assuming a miswiring model of parosmia, where incorrect OR expression in OSNs causes disruption of odour spatial maps at the OB glomerular level – see section on 'Qualitative Olfactory Dysfunction', subsection 'Parosmia – Pathophysiology').

In addition to the proposed mechanisms above, other factors may also contribute to C19OD. Inflammatory infiltrates have been demonstrated within human OE specimens [149,150], where upregulation of immune response-related genes has also been shown [148]. Chronic localised inflammation within the OE has also been demonstrated [151] and could have long-term effects: for example, persistent inflammation has been shown in genetically modified mice to cause functional shifts in OE stem cell populations from regenerative to immune phenotypes, with impaired neurogenesis [94,95].

In line with this and other upper respiratory tract infections, inflammatory oedema and physical obstruction of airflow to the OC, with associated transient OD, has been suggested in some patients [152,153]. However, a significant number of patients, particularly in early waves of the pandemic, experienced C19OD in the absence of perceived nasal congestion or rhinorrhoea [109,154]. Though speculative, there may be a cohort of patients in whom sufficiently localised oedema within the OC does not cause the sensation of nasal congestion. This theory is supported by computational nasal aerodynamics work in which changes in nasal airflow within the OC are not reflected by measures of gross nasal airflow [155]. Non-obstructive changes in OC airflow or changes in the absorptive qualities of olfactory mucus (including possible changes in the odour binding protein (OBP)) could also contribute to alteration of the complex spatiotemporal encoding of odour quality [49], though this remains to be proven.

Other mechanisms of damage to the OE may also include hypoxic injury secondary to coagulopathic/vascular pathology [156]. Of interest, the presence of chronic rhinosinusitis with nasal polyposis may be protective against COVID-19, due the down-regulation of sinonasal ACE2 expression caused by type 2 inflammation [157,158].

The role of central dysfunction in C19OD is less clear. Imaging studies have demonstrated transient oedema of the bilateral OBs in patients with C19OD [159,160]. MRI evidence for post-infectious inflammatory neuropathy has also been suggested [161], as well as reduced OB volume in patients with persistent C19OD [162–164]. Whether these findings are secondary to direct infection or para-infectious effects (including but not limited to inflammation, coagulopathic, or microvascular changes with secondary hypoxic injury) is unknown. It has been suggested that virion or subviral ribonucleoprotein complexes may pass from the infected OE to the central nervous system via transcellular or paracellular (e.g. via OEC compartments) routes [165], though the methodology of such work has now been questioned [166] and overall, evidence for the presence of virus within the CNS is inconclusive [147]. In some previous human cadaveric studies, higher viral RNA levels were demonstrated within the OB than other brain regions [165,167,168], and spike protein has been found in the OB of one patient [169]. However, it is now known that the S1 subunit of the SARS-CoV-2 spike protein can be shed during cell entry, and subsequently enter the systemic circulation. Neurons within the brain can take up such circulating spike proteins, confounding studies that use antibodies against the spike protein for viral localisation [170]. At present, evidence of active and replicative virion within the human OB is lacking, with perineural olfactory nerve fibroblasts potentially playing a protective role against neuroinvasion at vulnerable anatomical interfaces [171]. Similarly, definitive evidence of SARS-CoV-2 within brain regions upstream of the OB has not yet been found [147]. Persistent inflammation in the absence of detectable virion has, however, been demonstrated with hamster OB, where proinflammatory cytokines, microglial activation and a Type I interferon response was detected at >1 month post infection [172]. Such findings could be secondary to ongoing inflammation within the OE and may contribute to persistent C19OD. Interestingly, a recent study in patients presenting with a spectrum of COVID-19 neurological symptoms (ranging from anosmia to more severe symptoms), was unable to demonstrate associations between specific neurological symptoms or their severity and specific SARS-CoV-2 genomic signatures. The authors concluded that CNS manifestations in COVID-19 patients could be mainly linked to the individual inflammatory response, more than to specific viral features [173].

Whilst some of the above studies suggest mechanisms that may

contribute to early, transient or more long-lasting effects (e.g. as in Frere et al., and Zazhytska et al., [148,172]), the majority do not specifically aim to differentiate between acute and persistent disease. Persistent disease/PIOD should be diagnosed in line with post-COVID-19 syndrome ('long COVID') criteria at ≥3 months. In their recent study, Finlay et al., performed single-cell RNA sequencing of 3 biopsies and 3 brushings taken from the olfactory cleft of patients with persistent C19OD (confirmed with SIT testing at 4 months post initial infection) compared with a mixed group of controls [174]. Supporting immunohistochemical analysis, as well as olfactory mucus assays were available from separate patients. Across these different samples, the authors demonstrated increased T cell infiltrates (with interferon-γ expression) and an inflammatory shift in myeloid cell population. PIOD secondary to COVID-19 may, therefore, be associated with persistent inflammation at the level of the OE. While awaiting further confirmation, this is in keeping with earlier work, in which SARS-CoV-2 and increased inflammatory infiltrates were identified from OSN containing olfactory cleft brushing in 4 subjects with subjective OD of greater than 3 months duration(151). Continued work is required to delineate the ongoing pathophysiological mechanisms in PIOD, caused both by SARS-CoV-2 and other pathogens.
Possible mechanisms of qualitative OD will be discussed in the section on 'Qualitative Olfactory Dysfunction', subsection 'Parosmia/Phantosmia – Pathophysiology'.

Non-COVID-19-associated post-infectious olfactory dysfunction (PIOD)

In addition to SARS-CoV-2, upper respiratory tract infections with other viruses are a frequent cause of OD. Indeed, post-infectious loss has consistently been one of the most common presentations seen in specialist clinics [175,176]. Typically, women are affected more frequently than men, and are middle-aged or older at presentation [97]. The latter may be due to the reduced regenerative ability of the olfactory system with advancing age and the accumulation of previous insults [177]. The incidence of PIOD is higher in March or May, during which higher rate of influenza /parainfluenza virus type 3 infections are also reported [178,179]. Onset is usually sudden, and though patients may describe an unusually severe infection, some may be unaware of the causative episode. Such cases may therefore be incorrectly labelled as idiopathic. Often, patients are affected by parosmia and there is little fluctuation in olfactory ability over time [180]. Whilst post-infectious olfactory impairment can be permanent, this is often not the case. Indeed, it has been suggested that post-infectious olfactory loss improves more frequently than in other common aetiological subgroups [175]. In their 2006 prospective cohort study, Reden and colleagues demonstrated an improvement in the psychophysical test scores of approximately one third of 262 patients with PIOD (of duration ≥18 months) over an observation period of 14 months [181]. Whilst higher estimates of recovery have been quoted elsewhere in the literature [182], care should be taken in interpreting data based on patient self-reporting [183], or where patient numbers are limited [184]. It also appears to be important at what time point after the infection the patients entered the study.
A variety of pathogens may cause PIOD, including viruses, bacteria, fungi, or rare organisms such as microfilaria [16]. For purposes of discussion in this paper, PIOD refers to non-COVID-19 infectious aetiologies. Even prior to the pandemic, the most common of these was viruses, of which a wide variety have been linked with OD, including those causing the common cold, influenza and human immunodeficiency virus (HIV) [185,186]. However, the terminology post-infectious should be used preferentially as opposed to post-viral olfactory dysfunction to acknowledge the various causative pathogens within this group.

The pathophysiology of PIOD remains poorly delineated, but is thought to involve either damage to the OE or central olfactory processing pathways (mediated via direct transmission of pathogens to the brain through the olfactory nerve) [187,188]. With regard to the former, histological analysis in patients with PIOD shows neuroepithelial remodelling and replacement with respiratory type epithelium or occasionally metaplastic squamous epithelium [97,189]. The number of OSN cells is reduced, they are found in patchy distribution and their morphology may be altered: for example, they may be shrunken in size with dendrites that do not reach the mucosal layer. The associated number of receptors is also reduced [97]. Furthermore, OB volumes are reduced in patients with PIOD and correlate with residual olfactory function [190,191]. This likely reflects bulb plasticity, partly in response to reduced afferent input from the OSN of the neuroepithelium.

Olfactory dysfunction secondary to sinonasal disease

Rhinosinusitis is the main cause of olfactory loss due to sinonasal disease. This may be either acute, subacute or chronic rhinosinusitis (CRS). Whilst CRS is generally defined when symptoms persist for 12 weeks or longer, there is some variation in definition of the acute/subacute stages according to guideline used, as outlined below:

- EPOS-2020 [85]
    - o <10days = acute viral rhinosinusitis
    - o ≥10 days but <12 weeks = acute-post-viral rhinosinusitis (bacterial to be considered when specific clinical criteria met e.g. pyrexia over 38°C, severe local pain etc.)
    - o ≥12 weeks = CRS
- ICAR:RS [192]
    - o ≤4 weeks = viral URTI or acute bacterial rhinosinusitis
    - o >4 weeks but <12 weeks = subacute rhinosinusitis
    - o ≥12 weeks = CRS

Quantitative OD (in the form of hyposmia or anosmia) is a key diagnostic symptom for CRS [85,192,193]. Current guidelines classify CRS as primary or secondary, according to anatomical distribution (localised or diffuse) and endotype dominance (type 2 or non-type 2) [85]. Olfaction is most severely affected in patients with type 2 inflammation [194]. Accordingly, OD has been linked with endotypes that are characterised by severe nasal polyposis, tissue eosinophilia and aspirin-exacerbated respiratory disease (AERD) [195]. Central compartment atopic disease (CCAD) is a subtype of CRS (type 2) involving inhalant allergen sensitisation and inflammation of the central sinonasal compartment (middle and superior turbinates, posterosuperior septum) that has recently been associated with OD to a greater extent than other subtypes [196].

Previous guidelines classified CRS according to phenotypic subtype (CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP)) and this practice is continued in many studies. Where olfaction is considered according to this phenotypic classification, it is most affected by CRSwNP, followed by CRSsNP, non-allergic rhinitis, atrophic rhinitis, allergic rhinitis and chronic obstructive pulmonary disease [197–199]. Use of olfaction as a marker of inflammatory burden in CRS has been suggested [200].

With regards to allergic rhinitis, there is significant overlap in symptomatic presentation with CRS, which can cause difficulty in discriminating between the two conditions. Whilst OD may occur in allergic rhinitis, it is less prevalent (20 - 40% of cases, compared with 84% of CRS cases) and is less severe than in CRS [85,201]. However, the presence of OD appears to correlate with disease severity in allergic rhinitis, and recent work in paediatric populations has demonstrated the utility of OD as a marker for uncontrolled disease [202,203].

As outlined in the above section, OD due to CRS is likely caused by a combination of factors. These include: obstructed transmission of odourants to the OE caused by oedema, discharge ± polyps; short-term reversible ligand-OR inflammatory-mediated binding dysfunction [93,94]; longer-term neuroepithelium remodelling [97] and finally OB or upstream olfactory eloquent [1] brain region functional and/or structural remodelling [98–100,102].

OD associated with sinonasal disease tends to occur gradually, and fluctuates over time (204). It infrequently improves without treatment and is not commonly associated with parosmias [180,205,206]. Fluctuation as symptom, and its clinical value, has been re-examined recently and found to be a factor closely associated to CRS related OD. It is a symptom to be actively looked or asked for during patients history [207,208].
Given the high prevalence of CRS within the general population (10.9% in Europe [209]), it is likely that sinonasal diseases constitute the most frequent cause of OD, perhaps excluding C19OD [210,211] and not considering aging. However, such patients are often managed by their general practitioner or general ENT surgeons and are therefore less commonly encountered in specialist smell and taste clinics.

Post-traumatic olfactory dysfunction (PTOD)

Olfactory dysfunction secondary to traumatic injury is a major cause of permanent olfactory impairment and can be ascribed to one or more mechanisms. First, injuries affecting the nose may result in mechanical obstruction of odourants to the OE, through distorting nasal bone or septal fractures, direct neuroepithelial injury, blood clots, oedema or alteration in mucous characteristics [212]. The second mechanism involves transection, or shearing of the olfactory fila as they traverse the cribriform plate [103]. Such transection may occur with more severe coup/contra-coup type injuries, or with fractures of the midface/anterior skull base, with possible subsequent scarring that may limit axonal regeneration and targeting [213,214]. Finally, contusions, intraparenchymal haemorrhage or resultant gliosis may lead to dysfunction of the central structures involved in olfactory processing [104,215,216]. For example, localised contusion of the OBs [217], also 'scattered' (disintegrated) and/or irregular olfactory bulbs [218,219] following injury has been previously documented. However, PTOD can occur without any visible signs of trauma on imaging studies [104].

Patients with PTOD often describe sudden onset loss following their injury, however, presentation may also be delayed. Such delay may be in line with the patient first noticing their impairment when back in their usual environment. Alternatively, delayed presentation may reflect an underlying pathology that does not involve olfactory fila transection, but possibly central damage exacted through progressive mechanisms (e.g., oedema). Cognitive dysfunction over time may also lead to unawareness of chemosensory loss [220,221]. Increased subjective impairment, without increased rates of psychophysically proven OD, have also been demonstrated [222]. Following onset, fluctuation in function is infrequent and patients are often affected by phantosmia (and to a lesser degree, by parosmia) [180,223,224]. Evidence from several studies suggests that recovery is less frequent than in post-infectious loss and whilst prognosis is often poor, recovery may occur in approximately 30% of cases over time depending on the severity of the insult [175,181,225–228]. Recovery may involve central and/or peripheral mechanisms [229,230]. Finally, the presence of OD in patients with traumatic brain injury correlates with altered neuropsychiatric behaviour [231].

[1] 'Eloquent': anatomical brain regions which directly control neurological function, and for which neurological deficit may be observed following their damage.

Olfactory dysfunction associated with neurological disease

Over recent years, the link between OD and neurological disease has been increasingly recognised. Whilst such dysfunction has been associated with epilepsy [232,233], myasthenia gravis (234), schizophrenia and stroke [235], it is most commonly seen in neurodegenerative conditions such as Parkinson's disease and Alzheimer's disease [12, 236–238]. Indeed, evidence suggests that OD in Parkinson's disease (PD) is more common than the resting tremor and predates motor symptoms by many years [32, 239–242]. Furthermore, OD appears to be present in both genetic (specifically LRRK2-associated) and idiopathic PD [243].

Functional imaging studies have demonstrated reduced activity of the hippocampus and amygdala in response to odour stimuli in patients with PD compared with healthy controls [244]. Histological studies have shown deposition of pathological Lewy bodies in neurites within the central olfactory system, including the OB and tract, as well as decreased neuronal populations within the anterior olfactory nucleus [236,245]. However, the significance of such changes with regards to the wider neuropathology of PD remains to be fully elucidated. Whilst it has been suggested that the OE may offer an attractive target for diagnostic biopsies or brushings, several studies have shown no significant difference in immunohistochemical markers (including different synuclein subtypes) of OE in PD patients versus controls [246,247]. In addition, work by Huisman and colleagues indicates that there are an increased number of (inhibitory) dopaminergic neurons in the olfactory bulb which may explain, at least to some degree, hyposmia in PD patients [248] (but see also [249].

Patients with OD secondary to PD commonly describe a gradual onset, and may be initially unaware of their deficit. Such patients do not often report parosmia and are unlikely to see any improvement over time [180]. OD is not affected by treatment with anti-PD medications [250].

Olfactory dysfunction associated with exposure to drugs or toxins

Chronic exposure to toxins can result in OD. Pathogenic agents include heavy metals such as: cadmium and manganese, and pesticides, herbicides, and solvents. Chemotherapeutic agents and other medications should also be considered in this group. The pathological correlates of OD associated with toxin exposure may involve either peripheral, neuroepithelial, or central damage, the latter being facilitated through transport of toxins via the olfactory nerve [16].

Table 4 shows an abbreviated list of agents and medications that have been reported to affect olfaction. Although many medications have been reported to affect olfaction, carefully controlled data for the effects of such drugs on olfaction is limited.

Table 4. Abbreviated list of agents and medications that affect olfaction (adapted from ref [16,708–715]).

Agents	Medications
Acids	Anaesthetics (local)
Benzene	• Cocaine hydrochloride
Cadmium	• Procaine hydrochloride
Chlorine	• Tetracaine hydrochloride
Ethyl acetate	
Formaldehyde	Antimicrobials
Hydrazine	• Aminoglycosides
Hydrogen sulphide	• Macrolides
Lead	• Penicillins
Mercury	• Tetracyclines
Nitrous gases	• Terbinafine
Paint solvents	
Silicon dioxide	Anti-thyroid medications
Trichloroethylene	• Propylthiouracil
Zinc gluconate	• Thiouracil
	Chemotherapy
	Alpha-receptor antagonists

Congenital olfactory dysfunction

Certain genetic conditions are known to be associated with congenital dysfunction, most notably the developmental endocrine disorder Kallmann syndrome (hypogonadotropic hypogonadism). Typically, the diagnosis is made at an age between 12 and 16 years. The condition is associated with hypoplastic/aplastic olfactory bulbs and olfactory sulci, and OSN of varying number and maturity [97,251–253]. Such patients usually have anosmia, or severe hyposmia from birth. Recent work has also demonstrated olfactory, but not gustatory dysfunction in Turner's syndrome [254], and the Bardet Biedl Syndrome [255].

As MRI scanning becomes more common, non-syndromic hypoplasia/aplasia of the olfactory bulb is increasingly recognised. As such, the most frequent cause of congenital or 'developmental' anosmia is now thought to be isolated, non-syndromic, idiopathic congenital anosmia with no known genetic cause [256]. To make this diagnosis, the olfactory bulb structure should be hypoplastic or absent and the olfactory sulcus should be shortened (the sulcus is seen just above the olfactory bulb on coronal scanning) [257]. However, it should be noted that normal olfactory function has been demonstrated in the absence of MRI-demonstrable OB [47]. On the other end of the spectrum OB are present in congenital anosmia due to a mutation of the CNGA2 gene [258]. Following diagnosis, patients should undergo genetic, endocrinological and paediatric (if appropriate) evaluation in order to delineate the complete phenotype of the congenital dysfunction. As an exception to the rule, normal olfaction is also possible in the absence of MRI-demonstrable olfactory bulbs among left-handed women [47].

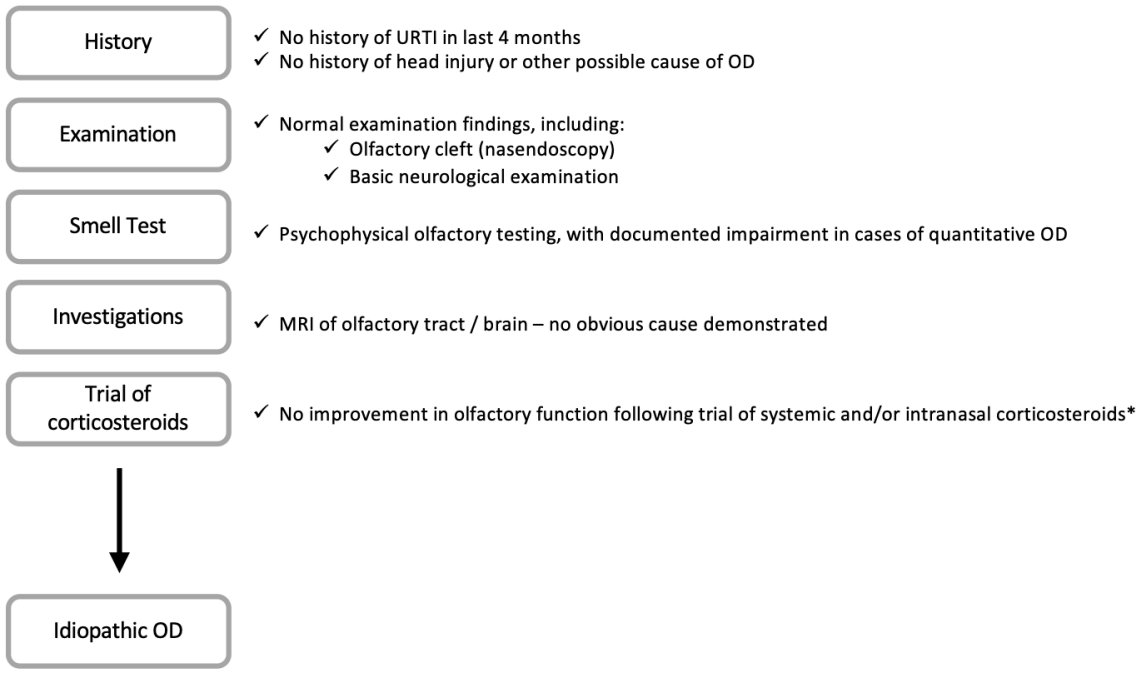

Figure 2. Criteria for diagnosis of idiopathic olfactory dysfunction.

Olfactory dysfunction associated with aging

As evidenced through epidemiological studies, olfactory function decreases with age, and age-related olfactory loss is the most frequent cause of OD (see 'Epidemiology of Olfactory Dysfunction' for more details). In addition to evidence linking it with mortality [10,11,40–42], OD appears to correlate with general health in the aging person, meaning it could be used as an early biomarker for age-related decline [36,39].

Previous work has suggested that olfactory loss with age is not homogeneous across smells: sensitivity towards unpleasant odours are usually preserved longer than pleasant ones, perhaps due to the formers' role in environmental navigation and defence [259].

The potential causes of olfactory impairment with advancing age are multiple and varied. A number of generic physiological changes occur within the nose of the aged that may affect olfaction, including parasympathetic/sympathetic dysregulation, reduced mucosal blood flow, fibrosis of the cribriform foramina and possibly also age-related mucociliary dysfunction. Moreover, age-related changes in the OE, OBs and central olfactory system also occur [260]. Changes in the OE and OB may be in part due to the reduced regenerative capacity of the OSN [177,261]. Recent work has suggested that age-related inflammation may lead to reduced OE stem cell differentiation [262]. In the absence of efficient OSN regeneration, damage from previous insults (e.g., upper respiratory tract infections and exposure to toxins) may accumulate to form permanent damage, which manifests as neuronal loss and stem cell reduction [63]. This results in a patchy distribution of OE in the aging nose, with associated decreased in number of OR. The reduced OB volumes seen with advancing age may be partially due to reduced afferent input (and consequent trophic effects) in line with OSN damage [63,99,263,264]. Rawson and colleagues showed that OSNs from subjects above 60 years of age lose their selectivity to specific odourants, instead responding to multiple odorants. This may impact the ability of older adults to discriminate odours [265]. Also of note, in the elderly, the number of medications taken can be inversely correlated with olfactory function (specifically with regards to odour threshold) [266].

Other disorders associated with olfactory dysfunction

Other disorders associated with OD may include intranasal or intracranial neoplasms, endocrine disorders (such as Addison's Disease, Turner's Syndrome or hypothyroidism), metabolic disorders such as diabetes mellitus, hypertension or vitamin B12 deficiency. Iatrogenic dysfunction due to surgery can be a complication of sinonasal surgery (e.g., septoplasty [267] or anterior skull base operations [16,268,269]), or surgery resulting in decreased airflow to the OC [270] (e.g. tracheostomy or laryngectomy [271]). Psychiatric conditions [272,273] and migraine [18,274] have also been

linked to dysfunction, as has radiotherapy [275] or alcohol dependence [276–278].

The role of smoking/nicotine in olfactory loss remains controversial. Several previous studies have demonstrated a dose-dependent, negative effect of smoking on olfactory function [44,279,280]. The underlying pathophysiology of this loss has been suggested to involve increased apoptosis of OSN [281] and/or replacement of the OE with squamous metaplasia [282]. However, other work has shown either negligible [283,284], or indeed protective effects [285] of smoking on olfaction. Work in rats has shown increased odour memory following treatment with nicotine agonists [286], and it has been postulated that this may contribute to the aforementioned protective effects [285]. Smoking also likely causes nasal inflammation, providing another mechanism for OD. Therefore, although it seems to be clear that smoking causes OD in certain cases, more research is needed.

Idiopathic olfactory dysfunction

Idiopathic OD is a diagnosis of exclusion. Studies suggest that up to 16% to 24% of patients screened at smell and taste centres fall into this category [287,288]. However, care should be employed when making this diagnosis, as some such cases may be due to asymptomatic upper respiratory infections, or in older patients – early neurodegeneration [242]. With respect to the latter, a multidisciplinary approach should be considered [289]. A trial of systemic and/or intranasal corticosteroids can also be useful in excluding otherwise undiagnosed inflammatory pathology, but – for systemic corticosteroids – should only be undertaken with appropriate patient counselling and consideration of contraindications (including, for example, diabetic status). Further studies are needed in this area, and as we understand more about the ways in which other underlying aetiologies affect the olfactory system, this category is likely to shrink substantially.

We suggest that the following criteria be fulfilled as a minimum, prior to diagnosis of idiopathic OD (for full details of clinical assessment, psychophysical testing and investigations, please see corresponding sections later in document, Figure 2).

Recommendations:

➢ Classification of olfactory dysfunction should be according to underlying aetiology (e.g., post-infectious, post-traumatic etc).

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

➢ Idiopathic olfactory dysfunction is a diagnosis of exclusion that should only be made following careful assessment, including normal MRI and exclusion of underlying inflammatory pathology.

o Delphi result: Agreed (score 7-9 = 93.5%, average score 8.5)

Qualitative olfactory dysfunction

Qualitative OD describes altered olfactory perceptual experience: parosmia involving the distortion of odour quality in the presence of a stimulus; phantosmia being the perception of odour in the absence of stimulus. Qualitative OD has been less researched than its quantitative counterpart and, whilst parosmia and phantosmia may co-occur, they are often grouped together in basic and clinical research, despite inherent differences in perceptual experience and variations in presentation rate. As the SARS-CoV-2 pandemic has progressed, however, a large cohort of patients with COVID-19-associated qualitative OD has emerged, making these conditions an important research priority.

Parosmia

Clinical presentation

Parosmia occurs when there is a mismatch between these patients' perceptual expectations (from their memory of an odour), and their actual experience. In general, distortions are described as unpleasant, though pleasant distortion ('euosmia') has been occasionally described [17,290]. Parosmia has been reported in 3.9% to 10% of the general population, and 7% to 56% of patients with OD [109,291–294]. Variation in patient prevalence rates occurs in relation to the specific OD population being sampled: parosmia appears to occur most frequently in patients with PIOD, followed by sinonasal, post-traumatic and idiopathic dysfunction [9,292]. Variance may also be associated with sample timing – for example, the online survey by Parma and colleagues captured C19OD symptoms within two weeks of illness onset, and found prevalence rates of less than 10% [109]. Conversely, Tognetti and colleagues reported parosmia in 49% of all COVID+ patients 18 months after initial diagnosis [133]. This is in line with reports that parosmia may occur several months after the onset of OD [9,139], and may be in keeping with a potential recovery period. Though the prognostic value of parosmia is debated, its occurrence during the recovery phase may be in keeping with the 're-wiring' pathophysiological hypothesis (described below). The majority of parosmic patients appear to have hyposmia (71%), followed by anosmia (22%) or normosmia (7%) [292]. Interestingly, however, Tognetti and colleagues demonstrated a larger proportion of parosmia in normosmic than hyposmic patients after COVID-19 (30% vs 20% respectively) [133]. In comparison to patients with quantitative OD, parosmic patients tend to be younger and more often female [9].

The psychosocial impact of parosmia appears to be far reaching: an exploratory thematic analysis of user-generated text from 9000 respondents within a social media charity support group (AbScent COVID-19 Smell and Taste Loss moderated Facebook group), identified marked impact on physical health (often surrounding altered eating, nutrition and weight [295]), psychological well-being, relationships and sense of self [140]. Indeed, it appears that patients with qualitative OD are more impacted than those with quantitative OD as manifest through: higher depression scores (Beck Depression Inventory) [296], reduced quality of life scores (Questionnaire of Olfactory Disorders) [297], and reduced ability to cope with OD [297]. Patients with qualitative dysfunction have been shown to report parosmia more frequently than phantosmia [7]. In line with this, recent data suggest that patients with parosmia have higher severity scores (composite score based on frequency and duration of distortion) than those with phantosmia [9].

Pathophysiology

The pathophysiology of parosmia remains unclear. Several models have been suggested, largely based on clinical presentation combined with existing knowledge and theories on olfactory system repair and odour quality encoding.

The quality of an odour is encoded through a complex spatio-temporal neural fingerprint. OSNs are monoallelic (i.e., express only one type of OR) and will therefore only respond to a characteristic set of odour ligands. In animals, OSNs are distributed stochastically within set zones of the OE, and the axon of each OSN type synapses within a set number of specific glomeruli within the OB. In this way (and ignoring the superadded complexities of nasal aerodynamics, odour absorption and OR-binding facilitation though OBP) it is thought that odour quality is spatially encoded at the level of the OB (though there may be some exceptions to this [47]). In animals, glomerular maps are established during embryonic development [298] and are subsequently stable throughout life [299]. Successful OSN repair or replacement, therefore, requires targeting of axons to the correct glomeruli within the OB [49].

The 'mis-wiring' hypothesis of parosmia speculates that incorrect odour quality is the result of incorrect or incomplete OSN – glomerulus synapse formation. This could occur in several ways, for example: 1) mistargeting of regenerating axons; 2) correct targeting of regenerating axons but switch in OR expression; 3) incomplete OSN population regeneration leading to partial odour maps. Several lines of evidence support the mis-wiring hypothesis, though definitive evidence in humans remains

lacking. In animals, damage to OSN can cause either delayed recovery or long-term damage to glomerular odour maps, depending on the mechanism of injury [214,224,300–304]. The behavioural impact of altered glomerular maps has also been demonstrated. For example, in hamsters that have recovered from surgical transection of the bilateral olfactory nerve, a period of retraining is required before they are able to perform discrimination assays in which they were competent pre-transection [223]. The authors of this work speculate that this is in keeping with relearning of odour quality due to altered glomerular maps. In humans, symptom onset timing provides circumstantial support for the mis-wiring hypothesis – parosmia tends to occur several months after the initial onset of OD, which is thought to coincide with formation of stable OSN-glomerular synapses [9,139,300].

Central models of parosmia have also been suggested, based on the following observations: 1) patients with parosmia have small OBs; 2) patients with parosmia have reduced grey matter (GM) volume in olfactory eloquent areas; 3) patients with parosmia have altered patterns of activation on functional magnetic resonance imaging (fMRI). Reduced OB volume has been demonstrated when comparing PIOD patients with parosmia to those without, despite similar quantitative olfactory function (305). Similar findings have also been demonstrated in mixed cohorts of patients with PIOD and PTOD [190]. The underlying cause of reduced OB volume in parosmia is unknown, though speculative causes could include reduced axonal input from peripheral OSNs, reduced OB interneuron populations/synapses or glial compartment changes. With regards to GM change, whole brain level analysis has demonstrated significantly reduced volume within the left anterior insula of parosmics, when compared with non-parosmics [306]. This is interesting, as the insula is a key node within the flavour network, which is thought to be involved in the central processing of disgust [307] and odour hedonic value [308,309], and more generally is an important part of the salience network (a system which integrates external sensory information with emotional and interoceptive input to determine stimulus salience [310,311]. Potentially in line with this structural finding, Iannilli and colleagues demonstrated increased functional activation within the insula (amongst other olfactory relevant areas) of hyposmic compared with parosmic patients. They additionally demonstrated increased activation within the thalamus and putamen of parosmic patients, compared to hyposmic [312]. This is again of interest, as the putamen has also been implicated in disgust processing, and the thalamus is thought to be involved in the attentional shifts, or 'thalamic gating' [313].

Other proposed mechanisms of parosmia include ephaptic firing – whereby aberrant 'short-circuit' transmission occurs between neurons in a way similar to that seen in epilepsy. This could possibly be due to demyelination of intracranial neurons, or damage to the OEC population at the periphery. Changes in the OB interneuron population could also cause hyperexcitability at this level. Such theories have anecdotal support through the successful treatment of some parosmic patients with anticonvulsant medications [314]. Other theories surrounding the physicochemical properties of particular 'trigger' odourants, and some unknown interaction with the damaged or repairing peripheral olfactory system have also been suggested [315]. The latter is supported by patient reports of particular odour types that commonly provoke parosmic responses (e.g. coffee, chocolate, meat, onion, garlic, egg and mint/toothpaste) [316,317]. Other changes – for example at the level of the OR population (during acute and/or regenerative phases) - are possible and have yet to be elucidated.

The interaction between proposed central and peripheral mechanisms of parosmia are unknown but these models are unlikely to be mutually exclusive. For example, reduced OB size may be the result of reduced or incorrect axonal input due to peripheral pathology, which could in turn lead to upstream structural and/or functional alterations within the central olfactory network. More work is required to delineate the pathophysiological processes at play, and their potential interactions, in both animal and human subjects.

Assessment

The diagnosis of parosmia is usually based on the patient's medical history [14]. Questionnaires may be of use, though their uptake in routine clinical practice has not yet been established. One such questionnaire from Landis et al., incorporated four questions focussing on: 1) altered perception of food; 2) persistence of malodour in absence of stimulus; 3) relative negative hedonic perceptual shift compared to other people; 4) alteration in odour quality, not strength [318]. Of the questions included, numbers 4 and 1 were most sensitive and specific in identifying parosmia. In addition to questionnaires focussing on perceptual experience, Hummel and colleagues proposed a scoring system that can be used for quantifying the severity of either parosmia or phantosmia, which can be used alongside other questionnaires, or medical history [319].

The first psychophysical tool ("Sniffin' Sticks" Parosmia Test – 'SSParoT') developed for the assessment of parosmia was recently reported by Liu and colleagues [320]. They developed a test in which odour pairs of opposite hedonic valence (pleasant and unpleasant) are presented to the patient, who is scored based on two metrics of hedonic perception: hedonic range (the perceived hedonic distance between two odours of opposite valence) and hedonic direction (indicator of overall hedonic perception of odours). Whilst this test was originally validated in 162 normosmic subjects, recent retrospective work using the

short version of the SSParoT in 63 patients with PIOD demonstrated poor sensitivity for the identification of parosmia, using either the hedonic range (sensitivity 29%) or hedonic direction (sensitivity 6%). The specificity of these two measures was better at 67% and 100% respectively. More work is needed to determine the utility of the extended SSParoT in clinical practice. Imaging should be performed in line with the suspected underlying pathology (see section on 'Clinical Assessment', subsection 'Structural Imaging'). In cases of clear PIOD, whilst volumetric imaging of the OB may help to confirm the diagnosis and give prognostic information, where resources are scare, or where volumetry is not routinely performed, MRI OB/brain may be omitted. With regards to other potential assessment tools, though differences in fMRI activation between parosmic and hyposmic patients have been shown [312], diagnosis based on single participant functional imaging is not advised, due to high levels of inter- and intrasubject variability.

Given the common co-occurrence of qualitative and quantitative OD, we would additionally suggest that quantitative ortho- ± retronasal olfactory function is assessed (please see section on 'Clinical Assessment', subsection 'Olfactory Testing - Psychophysical Testing').

Treatment options for parosmia have been traditionally limited, and based on clinician-specific, anecdotal evidence. Available evidence will be reviewed in the section on 'Treatment of Olfactory Dysfunction'.

Prognosis

Pellegrino and colleagues reported that, in comparison with quantitative OD and phantosmia, parosmia appears to be shorter lived and more likely to occur during recovery from an initial impairment. In line with this, patients are more likely to report improvement than in other forms of OD [9]. Other studies have also described parosmia during periods of recovery, with the majority of patients no longer experiencing parosmia after a period of approximately one year [291,292,321,322]. Whilst some studies have described greater recovery of quantitative olfactory function in the presence of parosmia [321,323], others have not [292]. However, it should be taken into consideration that the investigated groups vary, especially regarding duration of the olfactory loss at point of inclusion into the respective studies.

Phantosmia

Clinical presentation

Phantosmia is the perception of smell in the absence of an odour source (olfactory 'hallucination'). Similar to parosmia, patients with phantosmia usually describe their experiences as unpleasant, using terms such as 'burned', 'rotten', 'faecal', or 'chemical' [324], with 'smoky/burnt' being the most common descriptor in one series [325]. Phantosmia appears to be less prevalent than parosmia, affecting approximately 0.8 to 2.1% of the general population [326] (this figure rising to 6.5% of adults over the age of 40 [327], and has been as high as 31% in a small but randomly selected sample from Taiwan [294]), and up to 16% of patients with OD [9,292,325,328]. When coincident with parosmia, however, prevalence has been estimated in approximately one quarter of OD patients [291]. In comparison to patients with parosmia, those with phantosmia are more often anosmic (43%), though the majority of these patients, as for parosmia, are hyposmic (53%) [292]. The gender distribution also appears to be more balanced than in patients with parosmia (9), though a female preponderance has been suggested within the general population [325,327]. In comparison to patients with quantitative OD or parosmia, patients with phantosmia are more likely to be middle-aged [9]. Phantosmia is seen in patients with OD of varying aetiologies, including PIOD, sinonasal and iatrogenic OD, but appears to be most frequently reported in patients with PTOD [9,292]. Olfactory hallucinations are also reported in neurological and psychiatric conditions, for example, in temporal lobe epilepsy or migraine aura [2,329]. Unlike parosmia, phantosmia does not present as frequently during the proposed 'recovery' phase, indicating that phantosmia is not or less dependent on residual or changing olfactory function. As for parosmia, the impact of phantosmia on quality of life appears to be greater than in quantitative OD. Furthermore, Pellegrino and colleagues recently demonstrated higher levels of anxiety regarding environmental hazards and cleanliness and greater weight disturbance (with associated potential effects on physical health) in phantosmic than parosmic patients [9].

Pathophysiology

As for parosmia, the pathophysiology of phantosmia remains speculative. Existing theories are largely based on corollaries with the understood mechanisms of hallucinations in other senses, and the observation that phantosmia frequently occurs in PTOD, neurological and psychiatric conditions. However, it remains unclear whether phantosmia is due to purely central, peripheral or mixed central and peripheral mechanisms.

Epileptiform activity within the temporal lobe is known to cause olfactory hallucination (aura). In line with this, several studies have directly stimulated olfactory eloquent areas, including the OB, orbitofrontal cortex (OFC) and hippocampus. Holbrook and colleagues recently demonstrated subjective olfactory perception following transethmoidal electrical stimulation of the OB, in 3 out of 5 patients tested [330]. The elicited smells were generally unpleasant ('onion-like', 'antiseptic-like', 'fruity/bad'). Intracranial electrical stimulation of areas around the OB has also been performed during invasive surgical procedures being undertaken for epilepsy. In 2012, Kumar and colleagues elicited

subjective olfactory perception following subdural electrical stimulation of the ventral frontal lobe in 11 of 16 children [331]. More specifically, they elicited pleasant (n=9) or unpleasant (n=2) hallucinations following stimulation medial, but not lateral to the medial orbital sulcus (i.e., in areas proximal to the OB and tract on the gyrus rectus or medial OFC). More recently Bérard and colleagues elicited pleasant subjective olfactory perception in adult patients following stimulation of the bilateral OFC, but not the hippocampus, using stereotactically placed intracerebral electrodes [332]. Specific areas stimulated included the olfactory sulcus, medial OFC and medial orbital sulcus. The possibility that non-specific electrical stimulation of the OB could lead to unpleasant subjective odour perception is interesting: could phantosmia (± parosmia), which is usually unpleasant in nature, be due to aberrant electrical activity at the level of the OB? This is highly speculative and countered by the observation that olfactory aura in temporal lobe epilepsy is often unpleasant in nature.

The possible role of the OB in phantosmia has also been suggested in cases where surgical bulbectomy has proved curative in severe disease [333,334]. More peripherally, surgical excision of the OE has also been performed in a limited number of patients, with reported long-term success in the majority of cases [335]. Furthermore, histological abnormalities have been demonstrated within such surgically excised OE – including reduced mature OSN populations and axonal abnormalities [335]. Observations of symptom unilaterality, and relief with nasal obstruction or OE anaesthetisation have also been proposed to reflect peripheral aetiology [336]. Finally, peripheral dysfunction has been suggested by patient reports, where higher levels of nasal congestion and sinonasal disease are reported with phantosmia than parosmia [9]. Whether abnormality at the level of the OE itself could cause phantosmia, or whether such peripheral abnormalities lead to causative upstream dysfunction is, however, unknown.

As it stands, there is insufficient evidence to propose a definitive pathophysiological model for OD-related phantosmia. It is possible that both peripheral and central dysfunction may be involved, either together, or separately in different patients. Finally, care should be taken when equating proposed mechanisms of phantosmia associated with neurological or psychiatric disease with that occurring in the context of OD: these patients may form different cohorts based on divergent pathophysiology and required treatments.

Assessment

The diagnosis of phantosmia is based on the patient's medical history. The utility of structured questionnaires has been explored, but to date appear to be more sensitive to parosmia than phantosmia [318]. The severity score as described by Hummel and colleagues (see section 'Qualitative Olfactory Dysfunction', subsection 'Parosmia – Assessment and Treatment') can also be used in phantosmia [319].

As for parosmia, because phantosmia frequently occurs alongside quantitative OD, we would again suggest that ortho- ± retronasal olfactory function is assessed (please see section on 'Clinical Assessment', subsection 'Olfactory Testing – Psychophysical Testing').

Whilst imaging should again be performed in line with suspected underlying pathology (see section on 'Clinical Assessment', subsection 'Structural Imaging'), there is a lower threshold in phantosmia than parosmia. CT of the paranasal sinuses should be undertaken where there is suspicion of an endogenous odour source (suspected 'cacosmia' for example due to fungal sinusitis). MRI brain (including appropriate sequences for imaging of the OB) should be undertaken where there is suspicion of central pathology – for example in cases of PTOD or suspected temporal epilepsy.

Phantosmia associated with neurological or psychiatric disease should be treated as per the parent condition, with appropriate specialist consultation as required, ideally within a multidisciplinary setting. As in parosmia, treatment options for phantosmia associated with quantitative OD, or idiopathic phantosmia are limited, and based largely on anecdotal evidence. Again, available evidence will be reviewed in the section on 'Treatment of Olfactory Dysfunction'.

Prognosis

Phantosmia is not as frequently associated with recovery as parosmia. Rather, phantosmic patients are more likely to report that their condition was unchanged over time [9]. Landis and colleagues investigated long-term outcomes in 44 patients with idiopathic phantosmia and found that symptoms were gone or improved in 32% and 25% of patients, respectively, and unchanged or worse in 39% and 5% of patients, respectively [337]. Finally, the presence of phantosmia is not associated with increased rates of quantitative olfactory recovery [292,321,323].

Recommendations:

➢ The presence of parosmia or phantosmia, and their potential underlying causes, should be established through careful medical history.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)

➢ Structured symptom questionnaires, severity scores, and psychophysical olfactory tests may be used as adjuncts to diagnosis.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

➢ Due to their frequency of co-occurrence, assessment for

quantitative olfactory dysfunction should be undertaken when qualitative dysfunction is reported.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

➢ Imaging in qualitative dysfunction may be of use where there is suspicion of an endogenous odour source, or central pathology.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.6)

➢ Where a neurological or psychiatric cause is suspected, appropriate specialist input should be sought.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.8)

Clinical assessment

The initial clinical assessment of the olfactory patient is of vital importance: from the history alone a diagnosis can often be made. In this way, thorough clinical assessment is the foundation for full chemosensory assessment. Accurate diagnosis is required not just to guide management but also to give prognostic information [338]. This is particularly important in medico-legal cases.

When assessing patients with chemosensory impairment, one should bear in mind the close association of smell and taste [339]. Where a patient complains of reduced or distorted taste, often they are in fact suffering from olfactory impairment and describing consequent impact on flavour perception [176]. For example, the patient may be complaining of retronasal OD but unaware that they are also experiencing orthonasal impairment. Careful exploration to separate retronasal olfaction and gustation is required, particularly in the case of C19OD, where taste impairment may occur [109].

History

Thorough history taking should include [340]:

Specific impairment

Are patients describing a problem with their sense of smell, taste with respect to flavour, or taste with respect to basic gustatory attributes (sweet/salty/bitter/sour/umami)? Is their dysfunction quantitative, qualitative or both? If they are experiencing qualitative dysfunction, is this parosmia (stimulus present; parosmia absent when nares closed) or phantosmia (stimulus absent) or could there in fact be an internal stimulus, e.g., from the sinuses. If they are experiencing quantitative dysfunction, is this affecting all odours, or only specific odours, and how severe is their dysfunction in terms of frequency (i.e., daily or less) and intensity (i.e., anosmia or hyposmia)? What treatment have they had for their dysfunction to date, and has this been successful?

Onset

Sudden onset loss is more common in PIOD or PTOD, although in PTOD often there is a gap of days and weeks between the trauma and recognition of the deficit. Gradual onset is more often seen in sinonasal disease, neurodegenerative causes, and aging.

Duration

Dysfunction since childhood is likely to indicate congenital anosmia (and pertinent questions regarding other syndromic attributes should be considered). Longer duration of dysfunction may be a poor prognostic sign, particularly in cases of CRS and

PTOD.

Fluctuation
Olfactory function fluctuates markedly in cases due to inflammatory disease (CRS or allergy). Fluctuation may also occur in some, but not all cases of PIOD[180,341].

Other symptoms: sinonasal
Common symptoms of sinonasal disease (e.g., CRS, allergy) should be assessed, including nasal obstruction, rhinorrhoea, postnasal drip, facial pain, sneezing, and itching.

Other symptoms: non-sinonasal
Symptoms of the locally prevalent variant of COVID-19 should be assessed, including any temporal association with onset of OD. Symptoms suggestive of other systemic disease should also be considered.

Specific impairments and quality of life
Does the patient rely on their sense of smell professionally (e.g., chef, sommelier)? Is their dysfunction causing problems with interpersonal communication (particularly of note in mothers) or nutrition (including quantified weight change)? Does the patient describe anxiety or depression as a result of their dysfunction? If the patient is suffering from significant psychological effects, referral for assessment and management should be considered as appropriate. Does the patient live alone? If so, have they experienced any home accidents (e.g., fires, gas leaks etc.)? Such patients should be counselled regarding smoke and gas alarms and adherence to 'use-by' dates on foods.

Past medical history
Direct questioning should include previous head injuries, upper respiratory tract infections, sinonasal surgery or neurosurgery and any other chronic diseases that might affect olfaction (for example chronic kidney disease). Specific questions regarding symptoms of undiagnosed neurodegenerative disease should be considered in older patients where there is clinical suspicion. Such patients should be referred to neurological services as appropriate. Assess symptoms and contacts for COVID-19, if not done so already.

Medications
Current and previous medication history (including chemotherapies) should be obtained as well as compliance. The latter may be important where medications are required for control of chronic conditions (such as L-thyroxine in hypothyroidism). Where a patient has previously been treated with corticosteroids with improvement in smell, it is likely that they are suffering from sinonasal disease.

Allergies
Allergies to medications, seasonal, perennial and occupational environmental allergens should be assessed, as well as the treatment for these.

Smoking and alcohol
Current smoking and drinking may be associated with both reduced olfaction and taste.

Toxins and occupational exposure
Exposure to toxins known to cause OD should be assessed. Additionally, exposure to substances that increase the risk of sinonasal and nasopharyngeal carcinoma should be considered (e.g., softwood and hardwood dusts and sinonasal/nasopharyngeal carcinoma).

Family history
Family history of OD may aid in a diagnosis of congenital dysfunction. In older patients, a family history of neurodegenerative diseases should be assessed (including PD and Alzheimer's disease).

Recommendation:

➢ Thorough clinical histories should be sought from all patients.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.9)

Clinical examination

Examination should include a full ENT physical examination [2] . Nasal endoscopy should be performed, ideally with a 0° Hopkins rod lens endoscope (4mm diameter or smaller) to start. A 30° endoscope may then be used to facilitate visualisation of the OC, which is found in the superior nasal cavity, and bounded by the superior and middle turbinates laterally and superior nasal septum medially [67]. Whilst nasal decongestant should ideally be used (since meaningful examination of the nasal cavity is otherwise limited) [342], it should be noted that topical anaesthetic may cause temporary OD [343] and should therefore be avoided until after olfactory testing is performed.

Features to note on endoscopy include:

- General nasal anatomy including inferior, middle and superior meati.
- Visibility of OC, patency and any abnormalities thereof. Discharge, polyps, oedema, crusting, and scarring may be documented using the Olfactory Cleft Endoscopy Scale

[2] Please note, appropriate PPE should be used when examining a patient with confirmed or suspected COVID-19, particularly where endoscopy is undertaken, which is an aerosol generating procedure [338].

(OCES), which correlates with olfactory function in patients with CRS [344]. Signs of acute or chronic rhinosinusitis outside of the OC should be noted. Traditional endoscopic staging of the paranasal sinuses in CRS can be performed using the Lund-Kennedy scoring system [345].

- Other sinonasal abnormalities such as benign or malignant neoplasms. Where malignancy is suspected, a full examination of the mucosal surfaces of the head and neck should be undertaken, including thorough oral, pharyngeal and laryngeal examinations.

Where a neurological aetiology is suspected, a full neurological examination, including assessment of cranial nerves, and motor and sensory function should be undertaken. Tests of memory and cognition should be deferred to the appropriate neurological specialists [346], although appropriate screening tests may be performed if feasible.

When an asymptomatic patient requires assessment for medico-legal purposes, for example, prior to surgery (e.g. anterior skull base [269]), a full examination of the head and neck should be undertaken, including nasal endoscopy, though neurological examination can be omitted if appropriate.

Recommendations:

➢ Patients with suspected olfactory dysfunction should undergo a full ENT examination, including nasal endoscopy with careful inspection of the olfactory cleft.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.8)

➢ Basic neurological examination should be undertaken where there is suspicion of an underlying neurological aetiology, or in otherwise assumed idiopathic cases, though formal and detailed neurocognitive testing can be deferred to the appropriate specialists.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.7)

Olfactory Testing

The method used for assessing olfactory function is vitally important with respect to accurate diagnosis, outcome reporting and tracking of olfactory changes over time. A limitation of the current literature base is the heterogeneity of assessment techniques used, with consequent effect on definitions of impairment and improvement. As highlighted in the epidemiology section above, this can lead, for example, to large differences in estimated prevalence rates, and impacts significantly on the generalisability of results, especially where non-standardised and potentially unreliable tests are used.

In general, three different types of olfactory testing can be undertaken:

1. Subjective, patient-reported olfactory assessment.
2. Psychophysical olfactory assessment.
3. Olfactory assessment using electrophysiological studies or magnetic resonance imaging.

Again, when performing any assessment of olfactory function using the above methods, appropriate PPE should be worn where COVID-19 is confirmed or suspected (338).

Subjective assessment

Subjective testing can be performed using visual analogue scales, Likert questionnaires, or as part of other outcome assessments. For example, the commonly used SNOT-22 is a validated patient-reported outcome measure for CRS, which assesses overall disease burden. However, this contains only one question regarding OD [347]. Olfactory-specific patient-reported outcome measures, such as the Questionnaire of Olfactory Disorders (QOD), appear to have a greater ability to differentiate between patients with normosmia versus hyposmia than simple Likert questions such as those found in sinus-specific questionnaires such as the SNOT-22 and the Rhinosinusitis Disability Index [348]. For a recent systematic review of olfactory-related questionnaires and scales, see Han et al., 2021 [349].

However, as discussed briefly above, olfactory self-assessment tends to be unreliable and it has been shown that people do not perform well when compared to psychophysical testing [88,350–355]. In 2003, a group of healthy individuals were assessed for correlation between subjective, self-reported olfactory ability, and composite psychophysical olfactory test scores [355]. This study found that where subjective rating preceded psychophysical testing (using "Sniffin' Sticks"- see below), there was no significant correlation between the two. As outlined in the section on 'Epidemiology of Olfactory Dysfunction', accuracy in self-reported olfactory function does not appear to vary across age ranges [27], and the specificity of self-reported ratings is better than the sensitivity (87% and 31%, respectively) [28].

Poor approximation of self-rating to measured olfactory function has also been shown in patient populations. An early study by Delank and colleagues showed that 30-40% of CRS patients with impaired olfactory function rated themselves as unimpaired [351]. In a UK-based study of 80 patients presenting to a rhinology clinic, only 28% accurately reported their olfactory ability [350].

Whilst subjective assessment is useful in characterising the clinical effect of interventions, including the 'minimal clinically important difference/change' [356], given the above issues, these should not be performed in isolation. Rather, when diagnosing olfactory impairment, or assessing the effects of treatment, patient-reported outcomes should be used in conjunction with

more objective forms of assessment, as outlined below.

Recommendations:

➢ In patients reporting olfactory dysfunction, subjective olfactory assessment should be undertaken in order to fully determine quality of life and disease burden, as well as the clinical impact of interventions.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.6)

➢ When possible, validated questionnaires should be used. When this is not possible, a recognised form of assessment, possibly quantitative and/or anchored, such as a visual analogue scale, should be used.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.5)

➢ Subjective olfactory assessment should not be relied upon in isolation.

o Delphi result: Agreed (score 7-9 = 91%, average score 8.4)

Psychophysical Testing

Psychophysical tests provide a more reliable assessment of olfactory function than subjective reporting. Similar to an audiogram, during such assessment, an olfactory stimulus is provided and the outcome of the test is dependent on the patient's response. Psychophysical testing therefore requires a cooperative subject who can understand and follow instructions, as well as communicate choices to the clinician/investigator.

Orthonasal psychophysical tools

Through modification of psychophysical test type, different aspects of olfaction can be quantitatively assessed. Broadly, these different aspects can be divided into threshold and suprathreshold olfactory function.

Odour threshold is the lowest concentration of an odourant that a subject can perceive. Operationally, this is the concentration where 50% of stimuli are detected and 50% remain undetected. Odour threshold does not require specific identification of the odourant stimulus, rather a detection of 'something', usually in comparison to a blank, odourless stimulus. Where comparison is made between odourant and blank stimuli, some degree of short-term, working memory is required. However, this test is less directly related to episodic or semantic memory [357] and therefore has a lower cognitive burden.

Suprathreshold olfactory testing involves presentation of odour stimuli of sufficient concentration such that they should be detectable (i.e., above the threshold level) in an unimpaired person. By varying the odour presented, such tools allow for the testing of odour discrimination and identification abilities. Odour discrimination describes the ability to differentiate between different odours. Odour identification involves both recognition of a stimulus and communication of its correct identity (i.e., the ability to name an odour). Unprompted odour identification is difficult [358], hence most psychophysical tests incorporate either visual or written cues [359]. Unlike odour threshold, performance in the suprathreshold tasks of discrimination and identification correlate significantly with a subject's executive function and semantic memory [357]. Furthermore, tests of odour identification require previous exposure to odour stimulus, and may therefore be culturally specific (e.g., the well-known smell of wintergreen in the USA which is almost unknown in Germany). This also includes the idea that olfactory tests should be adapted to children (see below). For this reason, such tests must be validated in a local population and associated normative data collected before use.

The hedonic value of an odour as well as its relative intensity can also be considered forms of suprathreshold olfactory testing. Hedonic assessment of an odour, or how pleasant or unpleasant an odour is, does not require recognition or identification. However, there is a greater emotional component to these ratings and as such, episodic memory may be of greater importance compared with the other aspects of olfaction described above. Relative intensity can also be considered a form of threshold testing. Odour detection threshold is not to be confused with odour recognition threshold, which is the concentration of an odour required for recognition or identification. As this test involves identification of the odourant, it combines elements of both suprathreshold and threshold tasks. Hedonic value, intensity ratings and odour recognition thresholds are infrequently used during clinical diagnosis or outcomes assessment.

In addition, there are tests that rely on changes in breathing behaviour in relation to olfactory stimulation, e.g., the Sniff Magnitude Test [360] or the recording of respiratory patterns in relation to olfactory stimulation [361]. The Alcohol Sniff Test uses the distance of an odour source from the nostrils as a measure of olfactory function [362]. Subjects close their eyes, and an opened alcohol pad is placed 30 cm below the nose. With each exhalation the odour source is moved 1cm closer until the patient reports smelling alcohol. Whilst Davidson et al., demonstrated significant differences between patients and controls, and between patients with varying severity of OD, the day-to-day reliability and therefore utility of this test is dependent on the precise original protocol being used, including the correct concentration and opening of the alcohol pad. Where this is not done, the utility of this test in clinical practice is questionable. Furthermore, the high alcohol concentration used has significant trigeminal activity, possibly complicating its role as a test of olfaction.

The utility of testing for multiple psychophysical components of olfaction (e.g., threshold, discrimination and identification)

when assessing OD is debated. Previous work by Doty has suggested that different psychophysical tests measure a common source of variance, meaning that olfactory impairment and improvement may be effectively assessed using, for example, odour identification alone [363]. However, this theory is contradicted by other work. In 1988, Jones-Gotman and Zatorre described impairment of odour identification but not thresholds after selective cerebral excision [364]. Similarly, odour identification is affected by HIV dementia, whereas odour threshold scores are preserved [365]. Work by Whitcroft and colleagues demonstrated that the pattern of psychophysical test scores obtained in 1,226 subjects, with olfactory loss of varying cause, reflected underlying disease aetiology [180]. In this study, subjects with olfactory loss due to sinonasal disease were particularly impaired in their odour threshold scores, whereas patients with Parkinson's disease were preferentially impaired in suprathreshold olfactory tasks (odour discrimination and identification). Taken together, these studies suggest that olfactory threshold preferentially tests peripheral causes of olfactory loss (for example, due to sinonasal disease), whereas the suprathreshold tests of discrimination and identification preferentially assess central or cognitive causes of OD. Further data driven work using unsupervised machine learning in 10,714 subjects has identified three distinct clusters of subtest results which can be defined by odour threshold score [1) low threshold, good odour discrimination and identification; 2) very high threshold, absent to poor discrimination and identification; 3) medium threshold, preserved discrimination and identification] [366]. Whilst clear division of aetiology was not possible using these emergent clusters, there was overrepresentation of congenital OD within cluster 2 and PIOD within cluster 3. Therefore, assessing both odour threshold and suprathreshold tasks appears to add to the diagnostic value of the psychophysical tool.

Furthermore, the accuracy of psychophysical tools has been shown to increase when composite scores are used. In a study of 2,178 participants of mixed olfactory ability, the diagnostic sensitivity of the individual tests of odour threshold (T), discrimination (D) and identification (I) as compared with composite 'TDI' scores, were 64%, 56%, and 47% respectively [367]. These sensitivities increased where paired test scores were used but did not reach the diagnostic sensitivity of the full composite 'TDI' score. Using principal component analysis, this study further demonstrated that olfactory threshold scores individually explained more of the observed variance than odour discrimination or identification. However, these tests require additional time and staff for administration, so logistical issues may limit their use.

A variety of orthonasal psychophysical olfactory tests have been developed for clinical and research use. Some of these tests assess just one aspect of olfaction, whilst other assess multiple components [368,369]. For example, the well-known Smell Identification Test ('SIT/SIT-40', previously also known as 'UPSIT') is a reliable, standardised microencapsulated odour identification test, which has been adapted and validated for use in a number of different countries, as well as in children [370–373]. The SIT-40 does not require clinician supervision and is therefore very convenient. Accordingly, it is frequently used in the clinical setting, as well as in research [374–376]. The "Sniffin' Sticks" are another popular psychophysical test battery, in which the classical ('extended') version tests odour threshold and discrimination in addition to identification [377]. This tool utilises reusable odourant 'pens' which are presented to the subject by an examiner. A three-alternate forced choice paradigm is employed for odour threshold and discrimination, whilst odour identification is tested using four-alternate forced choice written/visual cues. Composite 'TDI' scores from the individual subtests are used in diagnosis, and higher scores indicate better olfactory function. Again, this assessment tool is reliable, has been validated in different countries, and normative data are also available for children [378–382], as well as a minimal clinically important difference (MCID, equivalent to a composite TDI score difference ≥ 5.5) [383]. Accordingly, Sniffin' Sticks are used extensively in research [241,384,385]. Other olfactory tests allow for the assessment of some, but not all components of olfaction. For example, the Connecticut Chemosensory Clinical Research Center Test (CCCRCT) assesses odour threshold and identification [386].

As mentioned previously, odour identification tests are culturally specific. Certain odours may not be familiar to those outside the country where the specific test had been developed. For this reason, normative data should ideally be collected from local populations [e.g., [387]] or alternatively local versions developed. [e.g., [370,371]]. Some attempts have been made to develop tests that would overcome geographic and possible genetic biases [388,389]. However, these tests have yet not been implemented in clinical routine.

Table 5 provides a non-exhaustive list of psychophysical olfactory tests which have been used in research and/or clinical settings.

Given the diagnostic utility of assessing multiple aspects of olfaction as described above, in combination with the apparent individual value of threshold testing, we suggest that psychophysical tools used in the comprehensive assessment of olfaction should ideally incorporate threshold testing as well as a test of suprathreshold function, for example, identification.

Recommendations:

➢ Psychophysical olfactory assessment tools should be reliable and validated for the target population.

Table 5. Different psychophysical tests available.

Psychophysical test	Olfactory components assessed
Full Orthonasal Tests	
"Sniffin' Sticks" (original version)	Threshold, discrimination, identification
Connecticut Chemosensory Clinical Research Center Test	Threshold, identification
T & T Olfactometer	Threshold, identification
University of Pennsylvania Smell Identification Test	Identification
Other Orthonasal Tests	
Scandinavian Odour Identification Test	Identification
Smell Threshold Test	Threshold
Olfactory Perception Threshold Test	Threshold
Barcelona Smell Test (BAST-24)	Odour detection, identification, memory
Snap & Sniff Olfactory Test System	Threshold
Orthonasal Screening Tests	
Smell Diskettes Test	Identification
Cross-Cultural Smell Identification Test	Identification
Pocket Smell Test	Identification
San Diego Odour Identification Test	Identification
Odourised Marker Test	Identification
Open Essence	Identification
Q-Sticks (3-item "Sniffin' Sticks")	Identification
"Sniffin' Sticks" (5- or 12-item version)	Identification
Brief Smell Identification Test (B-SIT; 12-item Cross-Cultural Smell Identification Test)	Identification
Quick Smell Identification Test (Q-SIT)	Identification
Novel Anosmia Screening at Leisure (3- and 7-item)	Identification
Barcelona Olfactory Test (BOT-8)	Odour detection, identification, memory
Paediatric Tests	
Smell Wheel	Identification
U-Sniff ("Sniffin' Sticks" paediatric version)	Identification
pBOT-6	Identification, threshold
Retronasal Tests	
Taste powders (20-item)	Identification
Candy Smell Test (23-item)	Identification
Candy Smell Screening Test (7-item)	Identification

o Delphi result: Agreed (score 7-9 = 98%, average score 8.8)

➢ Psychophysical olfactory assessment tools used in clinical and research settings should include tests of odour threshold, and/or one of odour identification or discrimination. However, we strongly encourage to test olfactory function by including two or three of these subcomponents.

o Use of other suprathreshold olfactory testing modalities can be considered, where such tests have been validated and have sufficient normative data.

o Delphi result: Agreed (score 7-9 = 91%, average score 8.3)

Olfactory testing in children

Measuring olfactory ability in children can be challenging since attention span can be limited and, for example, pairing of odour names with the smells may be age and location dependent [390]. However, olfactory tests have been successfully used in children as young as five, with successful completion of the test increasing with age. As an alternative, for very young and/or noncompliant children, the 'Smell Wheel' has been used successfully in children as young as four [391]. The smell wheel is an 11-odour game-like test in which odours are identified using words and pictures. A paediatric version of the "Sniffin' Sticks" (a 14 odour identification test) was developed in 2014 [392], with an internati-

onal updated version (12-item identification test, Universal Sniff Test, 'U-Sniff') described in 2018 [393]. The pBOT-6 is brief 6-item identification/threshold test that was recently validated for use in Spanish children [394].

Recommendation:

➢ When testing olfaction in children, the test should fit the motivation of the child, be culturally appropriate, and validated for the target age.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

Use of psychophysical tools to diagnose olfactory impairment

When using psychophysical tools to define olfactory impairment and improvement, it is important that reference is made to normative data collected for that test. Hyposmia can be separated from normosmia using the 10th percentile of normal test scores gathered from a population of young, healthy subjects [373,377,395]. Whilst age-related normative values should be known for the test in question (e.g. [395]), typically normosmia is related to young healthy adults. In contrast, anosmia is defined on the basis of the empirical distribution of scores obtained by anosmic people [378,396]. Whilst sex-related differences in psychophysical test scores have been demonstrated (women often outperform men [395]), diagnoses of impairment are not typically defined according to sex, but rather using values derived from mixed cohorts [373,377,395].

In a clinical setting, psychophysical testing is most commonly performed birhinally, where results represent the better of the two sides [355,397], and best reflect patient-level experience. However, evidence suggests that lateralised olfactory testing may serve both diagnostic and prognostic utility.

In 2007, Gudziol et al. reported results of monorhinal olfactory testing in 479 healthy controls, 765 patients with CRS and 53 patients with sinonasal or olfactory bulb neoplasms [398]. Using a 12-item screening version of the "Sniffin' Sticks" odour identification test, they found lateralised differences in function of 3 or more points occurred in 15% of controls, 26% of patients with CRS, and 32% of those with neoplasms. In 2010, Welge-Lussen and colleagues performed a similar study in 518 patients with OD of mixed causes [399]. Using the full Sniffin' Stick test battery they demonstrated significant lateralised differences of between 12.5 and 57.1%, depending on cause, the largest side differences being in patients with neoplasms. This study went on to demonstrate that lateralised differences in threshold score correlated significantly with lateralised differences in discrimination, identification and composite TDI scores. Work from Huart and colleagues demonstrated asymmetrical olfactory function (using the "Sniffin' Sticks" test battery) in patients with mild cognitive impairment, which could be used to efficiently differentiate these patients from those with post-infectious impairment or age-matched controls [400]. Imaging studies have additionally shown correlation between monorhinal test scores and ipsilateral olfactory bulb volume [401]. With regards to prognosis, follow-up work by Gudziol et al. showed that patients with lateralised olfactory differences were more likely to develop bilateral dysfunction than those without side differences [402].

Should lateralised olfactory testing be considered, even in a time-pressured clinical setting, psychophysical testing could begin with monorhinal odour threshold testing, or, for example, with the 32-item extended version of the "Sniffin' Sticks" identification test with 16 items being used for each side, or the 40-item SIT test with 20 items presented to each nostril. Where there is no significant difference in threshold score (e.g., for "Sniffin' Sticks" threshold <2.5 and identification <3 points) between the right and left sides, testing can continue birhinally. However, where a lateralised difference is present, full monorhinal testing should be performed.

Recommendations:

➢ Definitions of olfactory impairment should only be made with reference to normative values for the psychophysical olfactory test being used.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)

➢ Psychophysical olfactory testing should ideally begin with monorhinal odour threshold testing, if feasible. Where there is no significant difference in lateralised scores, testing may continue birhinally.

o Delphi result: Agreed (score 7-9 = 70%, average score 7.2)

Use of psychophysical tools to define clinically relevant change in olfactory function

The final consideration when using psychophysical tools to characterise olfactory function is the minimum test score change required to indicate clinical improvement or deterioration. This is particularly important when reporting the results of longitudinal prognostic studies and when assessing interventions: whilst there may be a statistically significant improvement in olfactory test scores following some form of treatment, this will not necessarily reflect an improvement in subjective disease burden, unless the change is of sufficient magnitude to be clinically relevant (i.e. has reached the MCID) [227,383]. For the "Sniffin' Sticks", the MCID has been defined as 5.5 for composite TDI, 3 for identification/discrimination and 2.5 for threshold [383]. The MCID for the SIT-40 has been taken as 4 (10% change) in several previous studies [403,404].

Recommendation:

➢ When reporting changes in psychophysical olfactory test

scores, improvement or deterioration in olfactory function should be defined according to established clinical correlates and target population for that olfactory test.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.5)

Psychophysical tests used in screening

In a clinical context, olfactory screening tests are often required for identification of potential impairment in asymptomatic subjects (for example, during pre-operative assessment for medico-legal reasons) [405]. Where screening is required, validated tools have been developed which allow for rapid differentiation between normal and impaired olfactory function. Such tests include the 12-item Cross-Cultural Smell Identification Test (also called the 'Brief Smell Identification Test' 'B-SIT') [406], the 12-item identification adaptation of the Sniffin' Sticks test [407], or the recently developed 8-Odourant Barcelona Olfactory Test (BOT-8), which tests threshold, memory/recognition and identification [408]. Where abnormalities are identified through screening, patients should then undergo full olfactory testing. Olfactory screening using dedicated psychophysical tools is felt to be preferable to subjective assessment alone, as self-reported symptom questionnaires are not as sensitive or specific as screening odour identification testing, particularly for mild hyposmia [409].

Where very rapid screening is required, for example, during large-scale population-based studies, tests using only a few odours have been developed. Again, these allow for separation of normosmia from OD, but do not allow quantification of OD (e.g., hyposmia vs anosmia). These include odour identification tests derived from the SIT-40 [the 3 or 4-item 'Pocket Smell Test' and 3-item 'Quick Smell Identification Test' ('Q-SIT') [410]] and the odour identification component of the "Sniffin' Sticks" [3-item 'Q-Sticks' [411,412] and a 5-item test [413]]. When using these tests, one should bear in mind the increased possibility of both false positives and false negatives. As outlined above, in a clinical setting, an abnormal test result using such tools should be followed by full psychophysical testing.

Recommendations:

➢ Screening for abnormal olfactory function in asymptomatic patients should be undertaken using validated psychophysical olfactory tools.

o Delphi result: Agreed (score 7-9 = 89%, average score 8.2)

➢ Patients with abnormal screening results should undergo full olfactory testing.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.5)

Home tests

As outlined above, it is well evidenced that subjective patient-reported olfactory function does not correlate well with psychophysical testing. Lack of accurate testing is problematic and may result in incorrect diagnoses and treatment plans, inaccurate outcomes measurement, inaccurate research data and limited patient insight into their condition. The need for validated, self-administered psychophysical tests has therefore become apparent during the course of the COVID-19 pandemic, where infection control issues have made testing impractical or impossible in many settings. Such tests may either be constructed by the patient at home or pre-prepared tests sent to their home by the clinician/researcher. In cases of the latter, in addition to self-administration, such tools must be relatively cheap and easy to transport. Some existing tests, including screening derivatives of the SIT-40 (e.g., B-SIT, Q-SIT or Pocket Smell Test), could therefore be included in this category.

Gupta and colleagues developed Novel Anosmia Screening at Leisure, a seven- (NASAL-7) and three- (NASAL-3) item self-administered odour identification test, based on common household items [414]. They demonstrated moderate accuracy in identifying patients with anosmia, anchored to SIT-40 testing [NASAL-7 AUC (area under ROC curve), 0.706; 95% CI, 0.551-0.862; NASAL-3 AUC, 0.658; 95% CI, 0.503-0.814]. A score of ≤7 on the NASAL-7 test was 70% sensitive and 53% specific in discriminating anosmic patients. A score of ≤2 on the NASAL-3 test was 57% sensitive and 78% specific. Other groups have also described the development of tests intended for use at home [415,416]. It remains to be seen whether these tests achieve wide-spread use.

Recommendation:

➢ When formal psychophysical olfactory testing is not possible (for example, in acutely infectious COVID-19 patients), validated home smell tests may be of use.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.3)

➢ Patients with abnormal results should undergo full olfactory testing.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.5)

Retronasal olfactory and gustatory testing

Gustatory dysfunction occurs less frequently than olfactory impairment. The ability to distinguish subtleties of food flavour relies heavily on retronasal olfaction, including features unique to the human oropharynx and inspiratory airflow [417]. Accordingly, when patients complain of 'abnormal taste', they are usually suffering from retronasal OD [176]. However, as mentioned above, careful exploration to separate retronasal olfaction and gustation is required. Where it is not possible to separate the two through patient report, retronasal olfactory and gustatory testing may be undertaken. This may be particularly useful in the case of C19OD, where smell and taste impairment may co-occur [109]. Such testing may also be of use in other situations in which there is diagnostic uncertainly. For example, it has been

demonstrated that in cases of sudden onset OD, such as PTOD, both orthonasal and retronasal functions decline concurrently. However, more progressive dysfunction, such as is seen in sinonasal disease, may preferentially affect the orthonasal route whilst retronasal olfaction may be preserved [418,419].

Several approaches have been described for testing retronasal olfactory function. In Japan, intravenous injection of chemicals that undergo pulmonary excretion has been used, with test outcome depending on presence/absence of perceived smell and latency of such perception [420,421]. More simply, retronasal olfaction can be tested by asking patients to identify flavoured solutions [422], powders (including pulverised foods and spices) [418], freeze dried gels [423] and candies [419]. There is some concern that the pure 'taste' components of these stimuli may confound results (e.g., identification of coffee through its associated bitter taste, rather than through the retronasal coffee aroma). In order to circumnavigate this, tests using 'tasteless' powders [424] or retronasal odour delivery devices [425] have been developed.

As part of a full olfactory assessment, screening of gustatory function should be undertaken. This can be achieved using liquids applied to the tongue separately for each of the different tastants. In practice, this is usually done for sweet, salty, sour or bitter. Whilst ideally umami should also be tested for, in practice it is poorly identified, reducing its utility in clinical practice [426,427]. Where any abnormalities are identified, full gustatory testing should be undertaken using validated tests with normative data [428–434]. Ideally, testing of retronasal olfactory function should also be undertaken.

In practice, where a patient complains of abnormal taste, it may be simplest to screen for gustatory dysfunction (as above), and where this is normal, progress to testing of olfaction as required.

Recommendations:

➢ Comprehensive psychophysical assessment should include gustatory screening for sweet, salty, sour, and bitter tastes in all cases.

o Delphi result: Agreed (score 7-9 = 80%, average score 7.7)

➢ Full gustatory testing should be performed where abnormalities are identified on screening or where it is not possible to differentiate between impaired gustation and retronasal olfaction. Accordingly, this should ideally include discrimination between retronasal olfaction (flavours) and gustatory (taste) abnormalities.

o Delphi result: Agreed (score 7-9 = 89%, average score 7.9)

Electrophysiology and Functional Imaging

Whilst subjective and psychophysical tools are sufficient for most clinical and research-based testing, olfaction can also be assessed in a less subjective way using electrophysiological and imaging studies.

Electrophysiological studies include electroencephalography

(EEG) and electroolfactograms (EOG - the recording of generator potential of OSN via an electrode in contact with the OE) [435–439]. As EEG and EOG are both event-related, delivery of a known concentration of odourant must be precisely controlled using an olfactometer, which therefore limits the use of such testing for clinical purposes [440]. Instead, EEG is useful in medico-legal assessment as well as in patients who might not be able to comply with psychophysical testing. EOG testing is limited to the research setting.

Functional imaging allows for the identification of brain activity in response to odour stimuli, and includes positron emission tomography (PET) and fMRI [441]. These techniques utilise changes in metabolism and cerebral blood flow, respectively, in order to map brain activity changes in response to stimuli [442]. However, the use of radioactive isotopes for PET makes this a less attractive technique, and fMRI has become more common. The use of olfactory functional imaging is again typically limited to the research setting.

Recommendation:

➢ Whilst electrophysiological and imaging studies are often reserved for research purposes, EEG-based olfactory testing can be useful for medico-legal purposes.

o Delphi result: Agreed (score 7-9 = 85%, average score 7.9)

Structural Imaging

Structural imaging may be undertaken during the assessment of patients with OD for diagnostic and/or prognostic purposes. However, there is considerable heterogeneity in practice between clinicians [443], and – outside of the context of CRS – no clear consensus in the literature regarding when imaging should be undertaken [444]. In the following section, we provide a brief discussion of the different structural modalities available, followed by recommendations for use according to aetiology.

CT

CT of the paranasal sinuses is commonly performed to delineate inflammatory pathology in the context of chronic rhinosinusitis. Its use in cases of clear CRS should be in line with existing guidelines [85]. Of note, volumetric techniques that assess opacification of the OC have been shown to correlate with olfactory function (odour identification scores) to a greater degree than traditional CT staging (Lund-Mackay score) in patients with CRSwNP, but not in patients with CRSsNP [445]. In cases where inflammation is not clinically suspected, CT scanning may reveal a small number

Table 6. – = not recommended. Please note that for qualitative OD (parosmia and phantosmia), the recommendations above are for idiopathic dysfunction – where there is an aetiology suspected (e.g., PIOD), imaging should be in line with this suspected aetiology. * Where not evident on endoscopy or if surgery is required/considered.

Suspected Aetiology	CT paranasal sinuses	MRI brain (including OB)
PIOD	-	Optional – OB imaging may provide diagnostic / prognostic information
Sinonasal OD	Recommended*	-
PTOD	Optional – may be considered when bony facial / cribriform plate injury suspected	Recommended
Neurological	-	Recommended
Drug/toxin related	-	-
Congenital	-	Recommended
Aging	-	Optional – may be of use when it is not possible to exclude early neurodegeneration
Iatrogenic	Optional – may be of use when OC/cribriform plate injury suspected	Optional – may be of use when intracranial pathology suspected
Idiopathic	Optional – may be of use to identify inflammation/OCS not otherwise diagnosed by endoscopy or trial of corticosteroids.	Recommended
Parosmia – unknown aetiology	Optional – may be of use to identify inflammation/OCS not otherwise diagnosed by endoscopy or trial of corticosteroids.	Recommended
Phantosmia – unknown aetiology	Recommended	Recommended

of additional cases: Mueller and colleagues demonstrated an additional 7 in a cohort of 101 patients with presumed non-sinonasal OD [446]. In patients in whom thorough endoscopic examination of the OC is not possible (e.g., due to high septal deviation), or in whom a diagnosis of idiopathic OD would otherwise be made, CT of the paranasal sinuses may be used to exclude underlying inflammation. An alternative approach in such patients would be to administer a trial of systemic and/or intranasal corticosteroids. Contraindications to corticosteroids and patient preference should be considered when choosing between these options.

CT of the paranasal sinuses/facial bones may also be of use in cases of PTOD or iatrogenic OD, where injury to the OC or cribriform plate is suspected. Additionally, such imaging may be informative in patients presenting with phantosmia of unknown aetiology – where an endogenous odour source due to sinonasal pathology (e.g., fungal sinusitis) may be demonstrated. Finally, CT imaging of the brain is often performed acutely in cases of head injury or cerebrovascular accident. Whilst gross abnormalities may be identified in this way, MRI is preferable for the investigation of intracranial pathology related to OD.

MRI

Magnetic resonance imaging provides superior visualisation of soft tissues compared to CT. Furthermore, coronal T2 sequences allow easy visualisation of the OB. Therefore, MRI is the modality of choice when investigating intracranial structures and pathology related to OD. Accordingly, in a recent survey of international practice, 15 – 31% of clinicians (depending on location) 'always' performed MRI of the brain/olfactory system during the initial assessment of OD as a presenting or isolated symptom, irrespective of suspected cause [443]. MRI in olfactory assessment can be used to provide diagnostic and prognostic information and is targeted at: 1) OB morphometry (volume and shape); 2) structures of the primary and secondary olfactory network; 3) olfactory sulcus (OS) depth.

OB volumetry can be performed using MRI. Adjusted for age and gender, the OB volume can be considered as normal, hypoplastic or aplastic. If the OB volume is taken at the 10th percentile of the distribution, an abnormal OB volume for a person (male/female) <45 years is less than 58mm^3 and for a person (male/female) >45 years is less than 46mm^3 [191]. Reduced OB volume has been demonstrated in patients with OD due to a variety of underlying aetiologies, including congenital OD, idiopathic OD, PIOD and PTOD, and have been linked to poor prognostic outcomes in the latter two [252,256,447–449]. Even in the absence of formal volumetry, grossly absent or atrophic OB may aid in the diagnosis of suspected congenital OD [216]. The presence of parosmia is additionally associated with reduced OB volume, independent of quantitative olfactory function, in patients with PIOD and PTOD [190,305]. In addition to reduced volume in disease states, OB volume has also been found to correlate significantly with olfactory function in many, but not all studies [161,190,191,305,450–452]. Potentially in line with this, prospective work in patients un-

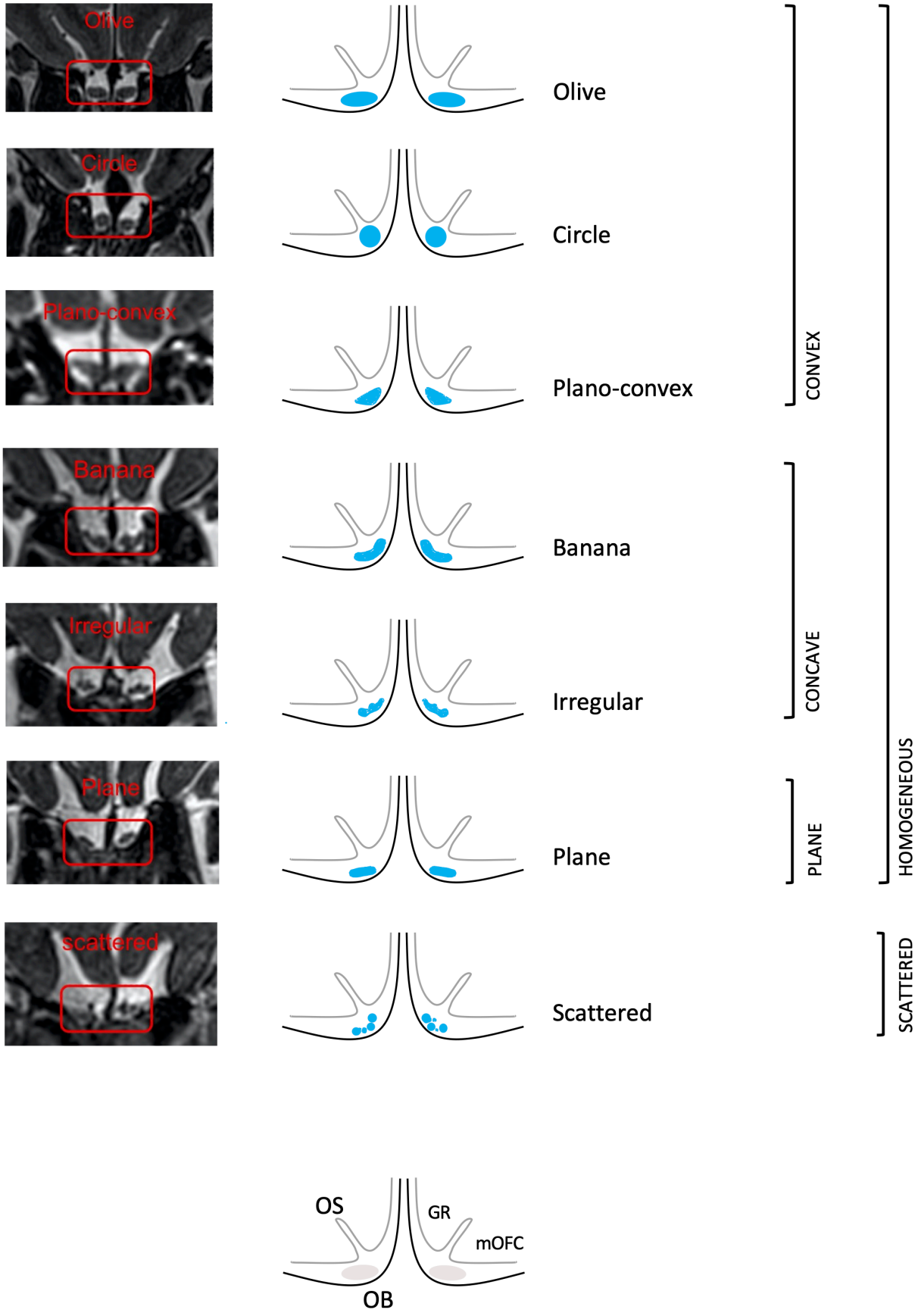

Figure 3. Olfactory bulb shape. Top – diagrams showing classification of OB shape (right) with radiological examples (left). Bottom – diagram showing location of OB (olfactory bulb), OS (olfactory sulcus), GR (gyrus rectus) and mOFC (medial orbitofrontal cortex).

dergoing surgical treatment for CRS has demonstrated increases in OB volume in association with improved olfactory function (specifically, odour threshold) [99]. Also in patients undergoing treatment for CRS, prospective change in right OB volume has been significantly correlated with change in GM volume within the ipsilateral orbitofrontal cortex [101]. OB shape has also been linked to olfactory function [191]. In a recent study of 192 patients (sinonasal, PIOD, PTOD, Parkinson's disease, idiopathic) and 77 healthy controls, 'non-convex' shapes were associated with significantly worse olfactory function (TDI score), independent of age, sex and OB volume [219]. Furthermore, irregular 'scattered' OBs, were seen significantly more often in PTOD. See Figure 3 for diagram showing classification of OB shape. Finally, however, it should be noted that olfactory perception has been demonstrated in the absence of radiologically evident OBs in women [47,453].

With this in mind, structures upstream of the OB should also be assessed. First, regions of the primary and secondary olfactory networks should be investigated for structural abnormalities, including potential neoplastic lesions and signs of neurodegeneration (e.g., cerebral atrophy). PTOD is often associated with abnormalities at the level of the OB, frontal and temporal lobes. Features such as orbitofrontal gliosis should be noted in these patients, as these are associated with poor prognosis and are therefore important for appropriate counselling. The pattern of brain lesions demonstrated following head injury can be used to predict the degree of OD, though this requires more complex scan interpretation [104].

Using specialist neuroimaging techniques, volumetric assessment of regions upstream of the OB has been performed. Accordingly, grey matter volume alterations have been demonstrated in structures of the primary and secondary olfactory networks, in patients with OD of various aetiology (PIOD, PTOD, idiopathic OD, sinonasal OD and mixed cohorts), compared with healthy controls [454–460]. Across these studies, the insula and orbitofrontal cortices appear to be the most frequently affected by OD, followed by the piriform cortex, anterior cingulate and parahippocampus. Structural plasticity in association with improved olfaction, following treatment for CRS or olfactory training in patients/healthy controls, has also been demonstrated [101,461–463].

Technical note:
Intracranial MRI should ideally cover the whole brain. The OB are best assessed using coronal T2 images, whilst other structures can be assessed using high resolution axial T1 images. With regards to the OB, possible imaging acquisition parameters are as follows: coronal scans, T2 weighted images, repetition time (TR) = 6770 ms; echo time (TE) = 84 ms; flip angle = 150˚; slice thickness = 1mm; field of view matrix = 263 x 350).

Furthermore, multimodal prospective neuroimaging work has demonstrated functionally significant structural plasticity within the orbitofrontal cortex, insula, anterior cingulate, and temporal pole, in association with improved olfaction after surgical treatment for OD [102,464]. At present, however, the use of such regions as personalised biomarkers of OD (in a similar way to the OB), has yet to be established – both within individual patients, and with regards to the complexity of imaging analysis required.

Finally, the depth of the OS has also been linked to olfactory function, with reductions demonstrated in patients with PIOD and congenital OD, as well as some, but not all patients with PTOD and idiopathic loss [161,253,256,257,344,465–469]. The OS demarcates the division between the medial orbitofrontal gyrus and the rectus gyrus. It can be relatively easily identified and measured on coronal images (in the plane of the posterior tangent through the eyeball), making it an easy target for clinical assessment. It should be noted that the right OS is larger than the left under normal circumstances [470].

Despite the above, there is debate in the literature regarding the diagnostic utility and therefore cost effectiveness of MRI scanning. In a study of 247 patients with idiopathic OD (of whom 54.9% were scanned), only 0.8% had OD that could be attributed to abnormalities seen on imaging [471]. The authors therefore argued that such scanning was not cost-effective. However, in another study of 122 patients with idiopathic OD, intracranial neoplasms were demonstrated in 4.9% of patients. These authors argued that medical malpractice costs associated with missed intracranial neoplasms were sufficient to justify MRI for idiopathic OD [472]. In line with this, the most common reason for scanning in the recent ICAS survey was to 'exclude neoplasm' [443]. We provide recommendations for ideal scanning practice according to aetiology below. However, we acknowledge that these recommendations will necessarily be interpreted through the lens of local healthcare systems, wider economic burdens, and individual clinician preference.

Recommendations:

➢ Structural imaging should be undertaken according to suspected underlying aetiology (see table 6).

➢ In idiopathic olfactory dysfunction: CT of the paranasal sinuses is optional and may identify inflammation not otherwise diagnosed by endoscopy or trial of corticosteroids; MRI brain is recommended.

o Delphi result: Agreed (score 7-9 = 91%, average score 8.3)

➢ CT should be performed as first line imaging of the paranasal sinuses when sinonasal inflammation or bony abnormalities are suspected. MRI should be performed as first line when intracranial abnormalities are suspected, or morphometry of the OB is required.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.8)

Treatment of olfactory dysfunction

Despite considerable efforts within both the clinical and research communities, long-term, effective treatments for OD largely remain elusive [473–478]. The current literature base is limited by lack of high-level evidence (e.g., from large-scale randomised control trials), likely due to historical lack of funding, insufficient study participants, and inherent methodological and/or hypothesis driven differences that prevent generalisation of results. However, the devastating impact of the COVID-19 pandemic has focused efforts and attracted funding towards PIOD. The whole arena of OD will likely benefit from such ongoing work.

In the following sections we will outline the more common, or more successful interventions currently available and their evidence base. Following this, we will present evidence and rationale for more novel treatment approaches.

Medications

In the following sections we will review evidence for the use of corticosteroids, monoclonal antibodies, phosphodiesterase inhibitors and intranasal calcium sequestrants. Other medications are covered either in the 'Novel Treatments' subsection, or in Table 7. Treatment of qualitative OD is covered in the 'Treatment of Qualitative Olfactory Dysfunction' subsection.

Delivery Mechanism for Intranasal Medications

As outlined in the earlier section '**Anatomy and Physiology of Olfaction**', the precise extent of the OE is debated, and likely varies between patients. However, it would appear that OE can consistently be located immediately below the cribriform plate [62]. Effort has therefore been made to facilitate delivery of intranasal medication as high into the OC as possible, using various approaches, including head positioning, varying drug preparations and specialist application devices.

The 'Kaiteki' position describes a position in which the patient lies laterally, with their head rotated (away from the bed/recumbent shoulder to the 'upwards' side) by 20-30 degrees, and with their neck extended by 20-40 degrees [479]. Instillation of intranasal medication to the upper nostril (i.e., contralateral nostril to the recumbent shoulder) in this position appears to improve access to the OC, particularly when the nasal cavity has been decongested. Other positions appear to confer little benefit in directing medications towards the OC [480,481]. With regards to drug preparation, nebulisation, atomization or delivery of drops diluted in intranasal douches (irrigation/rinses) appear to improve access to the OC [482,483]. Application devices such as the 'squirt system' (which utilises a thin cannula affixed to a syringe, and which allows application of a high pressure stream directed towards the OC) or the liquid Exhalation Delivery System (which enables positive pressure delivery of intranasal medication with a closed nasopharynx through patient exhalation [484]) have also been shown to facilitate improved access to the OC, though their use is dependent on funding/availability.

Corticosteroids

Corticosteroids are a mainstay in the treatment of CRS, though their recommended use differs according to endotype/phenotype (with olfaction being more prominently affected in CRSwNP/Type 2 inflammation, as outlined in **Olfactory dysfunction secondary to sinonasal disease**). With regards to OD secondary to CRSwNP/Type-2 inflammation, evidence exists to support use of corticosteroids, with efficacy varying according to route of administration [86,385,485–491]. The duration of benefit from systemic corticosteroids may be limited, with return to baseline often seen within 3 months [492]; repeated use may be limited by the risk of adverse events, and intranasal corticosteroids therefore play a more important role in first line maintenance therapy. As outlined above, different ways of maximising drug delivery to the olfactory cleft have been explored – including use of particular head positions, dilution of medication into irrigation solutions, and special devices such as the liquid Exhalation Delivery System (see **Delivery Mechanism for Intranasal Medications** for full discussion). Extensive guidelines exist for the management of CRS, and use of corticosteroids therein [85,92,193,492–498]. We would refer you to these guidelines for detailed management of these patients.

With regards to non-CRS-related causes of OD, the literature base is less robust, and it is more difficult to draw firm conclusions regarding the utility of corticosteroids in such patients. However, there is some rationale for their use: for example, long-term inflammation in the OE of C19OD animal models has been demonstrated and such processes may contribute to persistent olfactory impairment in both COVID-19 and non-COVID-19 PIOD (499). The following outlines available evidence for use of systemic and topical corticosteroids in the non-sinonasal disease OD patient group.

Systemic corticosteroids

Several studies have addressed the use of systemic corticosteroids for the treatment of PIOD. An early study from Ikeda and

Table 7. Summary of current clinical and experimental evidence for medication therapy in olfactory dysfunction.

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
COVID-19-associated Olfactory Dysfunction								
Corticosteroids	Le Bon et al. [502]	2021	Prospective, controlled	Oral methylprednisolone (32 mg OD) + OT (n=9); OT only (n=18) Duration: 10 days (oral methylprednisolone); 10 weeks (OT)	Patients with C19OD; n=27	Change in Sniffin' Sticks (TDI) scores after 10 weeks	Yes (p=0.046)	Significantly higher increase in composite TDI scores in those who received oral corticosteroids compared to controls
Corticosteroids	Vaira et al. [683]	2021	Prospective, case-control	Oral prednisone (1 mg/kg/day tapering for 15 days) + intranasal betamethasone irrigation + ambroxol + rinazine (n=9); No treatment (n=9) Duration: 15 days	Patients with COVID-19-associated anosmia or severe hyposmia; n=18	Change in CCCRCT score at 20 and 40 days after	Yes (p=0.011 at 20 days, p=0.024 at 40 days)	Significantly higher CCCRCT scores for the treatment group at 20 and 40 days, compared to control
Corticosteroids	Kasiri et al. [523]	2021	Prospective, controlled	Intranasal mometasone furoate spray (2 puffs, 100 µg BID in each nostril) + OT (n=39); intranasal sodium chloride (2 puffs BID) + OT (n=38) Duration: 4 weeks	Patients with COVID-19- associated severe anosmia or microsmia; n=77	Change in Visual Analogue Scale (measured weekly), Iran-SIT after 4 weeks	No (Iran-SIT) Yes (VAS at week 1, 2, 3, and 4, p<0.001)	No significant difference in mean odour identification score after 4 weeks, but significantly more patients in the intervention group regained their normal sense of smell (p<0.001)
Corticosteroids	Abdelalim et al. [524]	2021	Prospective, controlled	Intranasal mometasone furoate spray (2 puffs, 100 µg OD in each nostril) + OT (n=50); OT only (n=50) Duration: 3 weeks	Patients with C19OD; n=100	Change in Visual Analog Scale (0 to 10) scores (measured weekly)	No	No significant difference in VAS scores between the treatment and control groups, but statistically significant improvement in smell scores in both groups after 3 weeks (p<0.001)
Post-infectious Olfactory Dysfunction (Non-COVID-19)								
Corticosteroids	Kim et al. [521]	2017	Retrospective, case series	Oral prednisolone (40 mg x 14 days, tapering by 5 mg daily) (n=60); intranasal mometasone furoate monohydrate spray (2 puffs, 100 µg in each nostril OD) (n=181); Oral prednisolone + intranasal mometasone spray (n=250) Duration: 16 days (Oral prednisolone), 1 month (Intranasal mometasone)	Patients with olfactory dysfunction of mixed causes; n=491 178 PIOD 96 PTOD 94 Sinonasal 89 Idiopathic 23 Post-Sinonasal Surgery 9 Xerostomia 2 Congenital	Change in CCCRCT, CCSIT, subjective rating (recovery vs. no recovery) 1 month after treatment	Yes (p<0.001)	Oral + intranasal and oral corticosteroid groups had better smell recovery outcomes than the intranasal group, No significant difference between oral + intranasal versus oral only (p<0.978)
Corticosteroids	Fleiner et al. [520]	2012	Retrospective	Topical corticosteroid (unspecified drug / dose) + OT (n=18); OT only (n=28) Duration: unspecified	Patients with olfactory dysfunction of mixed causes; n=46 16 PIOD 15 Sinonasal 8 Idiopathic 7 PTOD	Change in Sniffin' Sticks (TDI) scores at 4 or 8 months	Yes (p=0.001 at 8 months)	Statistically clinically significant improvement in TDI scores in the topical corticosteroid + OT group after 8 months of treatment
Corticosteroids	Heilmann et al. [519]	2004	Retrospective	Intranasal mometasone spray (2 sprays OD, ~0.1 mg per nostril) x 1 to 3 months) (n=37); oral prednisolone (40 mg/day, tapering doses over 21 days) (n=55) Duration: 1 to 3 months (Intranasal mometasone), 21 days (Oral prednisolone)	Patients with olfactory dysfunction of mixed causes; n=92 58 Idiopathic 22 PIOD 12 Sinonasal	Change in Sniffin' Sticks (TDI) scores after 21 to 330 days	Yes (p<0.001)	Treatment with oral prednisolone led to significantly improved TDI scores regardless of aetiology (p<0.001), intranasal mometasone had no significant effect on olfaction
Corticosteroids	Nguyen & Patel [522]	2018	Prospective, controlled	Intranasal budesonide irrigation (0.5 mg/ 2 ml BID) + OT (n=66); Intranasal saline irrigation (BID) + OT (n=67) Duration: 6 months	Patients with olfactory dysfunction of mixed causes; n=133 62 PIOD 46 Idiopathic 16 PTOD 6 Medication-related 3 Environmental exposure	Clinically significant change in SIT-40 after 6 months	No	Clinically significant change in SIT-40 scores in 35.3% of patients (n=47), Younger age and shorter duration of OD were associated with improvement (p<0.0001)

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Corticosteroids	Stenner et al. [509]	2008	Retrospective	Oral beclomethasone (3 to 0.5 mg OD to TID) + topical budesonide (1.5 mg/day, divided into 2 equal doses per side of the nose BID); oral beclomethasone + topical budesonide and neomycin (7.5 mg/day, divided into 2 equal doses per side of the nose BID) Duration: 20 days (Oral beclomethasone), 12 weeks (Topical budesonide only or with Neomycin)	Patients with olfactory dysfunction of mixed causes; n=89 31 PIOD 22 Idiopathic 16 Sinonasal 14 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after 12 weeks	No	No significant difference between TDI scores of treatment and control groups, Improved mean TDI scores with oral steroids across all treatment groups, with benefit from topical corticosteroids +/- antibiotic influenced by initial oral steroid responsiveness
Corticosteroids	Blomqvist et al. [518]	2003	Prospective, controlled	Oral prednisolone (40 mg/day x 3 days, tapering by 5 mg daily), then either Intranasal fluticasone spray (2 sprays, 100 µg OD in each nostril) (n=20); placebo spray (water, avisel, polysorbate 80, glucose, benzalkonium chloride (198 µg/g) and phenyl ethyl alcohol (2.5 mg/g) (n=10); no treatment (n=10) Duration: 10 days (Oral prednisolone), 6 months (Intranasal fluticasone, placebo)	Patients with olfactory dysfunction of mixed causes; n=40 23 PIOD 10 Sinonasal 7 Unknown/Idiopathic	Change in CC-CRCT, VAS after 10 days, 2, 6 months)	No	Significant improvement after the initial treatment with oral corticosteroids, no significant difference in olfactory threshold scores between treatment and control groups after 10 days, 2 and 6 months
Corticosteroids	Schriever et al. [510]	2012	Retrospective	Oral methyl-prednisolone (40 mg, then tapering by 5 mg every other day) Duration: 15 days	Patients with olfactory dysfunction of mixed causes; n=425 221 Sinonasal 157 Idiopathic 27 PIOD 20 PTOD, Post-surgical, Others)	Change in Sniffin' Sticks (TDI) scores after 15 days	No control group	Greater and clinically significant increase in TDI scores among patients with nasal polyps (p<0.001) who received treatment, PIOD (p=0.003) and idiopathic (p=0.01) patients who received corticosteroids also significantly improved but the improvement was less than those with sinonasal causes
Corticosteroids	Fukazawa [501]	2005	Prospective	Dexamethasone (5 mg every 2 weeks) septal injection; betamethasone (5 mg every 2 weeks) septal injection Duration: 8 to 10 times	Patients with PIOD; n=133	Change in T&T olfactometer, Visual Analogue Scale	No control group	49.6% of patients achieved improvement in recognition threshold, VAS improved from 10.2 to 39.5
Corticosteroids	Heilmann et al. [513]	2004	Prospective	Oral prednisolone (40 mg/day, tapering doses over 21 days) (n=85); intranasal mometasone (2 sprays OD in each nostril) (n=76); oral Vitamin B complex (thiamine 12 mg, riboflavin 12 mg, pyridoxine 0.75 mg, nicotinamide 60 mg, calcium pantothenate 6 mg 2 capsules TID) (n=31) Duration: 21 days (Oral prednisolone), 6 months (Intranasal mometasone and Vitamin B complex)	Patients with olfactory dysfunction of mixed causes; n=192 85 Idiopathic 72 PIOD 19 Sinonasal 10 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after an average of 2 and 6 months	No control group	Improvement following oral and intranasal corticosteroids (p<0.001, p=0.03 respectively); improvement with oral Vitamin B only after 6 months (p=0.001) but not after 2 months (p=0.07)
Corticosteroids	Ikeda et al. [500]	1995	Non-controlled	Intranasal betamethasone (few drops of 0.1% solution to superior nasal cavity in Kaiteki position) (n=5) or beclomethasone dipropionate (aerosol, 400 mg/day) (n=16); then oral prednisolone (40 to 60 mg/day tapered over 10 to 14 days	Patients with sinonasal and PIOD; n=21 12 Sinonasal 9 PIOD	Change in T&T olfactometer threshold	Yes (Detection: p<0.05, Recognition: p<0.01 for sinonasal)	Significant improvement in T&T olfactometer detection and recognition thresholds for sinonasal group but not for post-infectious group

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Phosphodiesterase Inhibitors	Hosein & Henkin [551]	2022	Prospective	Intranasal theophylline (20 µg in 0.4 ml saline solution, 1 spray OD, with increasing dosage if no improvement after 2-4 months after to a maximum of 4 sprays / day) (n=39), placebo (saline) (n=39), normal (n=17) Duration: at least 2 months	Patients with normal olfactory function and hyposmia from multiple causes; n=56 12 PIOD 7 Sinonasal 9 PTOD 5 Idiopathic 3 Chemical Exposure 3 Congenital	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)) after at least 2 months of treatment	Yes (DT: all odours, p<0.01, RT: Pyridine p<0.005, Nitrobenzene, Thiophene, Amyl Acetate p<0.01)	Over half of treated patients experienced a decrease in nasal mucus IL-10 toward control levels after intranasal theophylline administration, correlated with a significant improvement in taste and smell function
Phosphodiesterase Inhibitors	Henkin et al. [554]	2012	Prospective, internally controlled	Oral theophylline anhydrous (200 to 800 mg/day x 2 to 12 months; intranasal theophylline methylpropyl paraben 20 µg/day in each naris x 4 weeks, controls were same group	Patients with olfactory dysfunction of mixed causes; n=10 3 Sinonasal 3 PIOD 2 PTOD 1 Congenital 1 Other	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100)	Yes (DT for Sucrose and Hydrochloride (p<0.01), and Urea, (p<0.05))	Intranasal theophylline treatment improved taste and smell acuity in 8 of 10 patients after 4 weeks, Oral theophylline treatment improved taste and smell acuity in 6 of 10 patients after 2-12 months
Phosphodiesterase Inhibitors	Henkin et al. [550]	2017	Prospective	Oral theophylline (200 to 800 mg taken over 2 to 10 months) (n=44)	Patients with hyposmia from multiple causes; n=44 15 Sinonasal 10 PIOD 9 Congenital 8 PTOD 1 Post anaesthesia 1 Oropyrosis/Dysgeusia	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective improvement in smell/ taste/flavour (0 to 100)	No control group	Significant improvement in subjective responses in smell (p<0.05), taste, and flavour perception and in olfactometry, associated with increased nasal mucus sonic hedgehog and serum theophylline after treatment
Phosphodiesterase Inhibitors	Henkin et al. [553]	2009	Prospective	Oral Theophylline in increasing doses (200, 400, 600, and 800 mg) over 2-8 months	Patients with olfactory dysfunction of mixed causes; n=312 97 PIOD 97 Sinonasal 76 Others 42 PTOD	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100) daily	No control group	Subjective smell loss improved in 157 patients (50.3%), Greater improvement in mean DT and RT before and after treatment (DT: Pyridine (PYR) (p<0.001), Nitrobenzene (NO2B) (p<0.05), Thiophene (THIO) and Amyl Acetate (AA) (p<0.01); RT: PYR and NO2B (p<0.001), NO2B, THIO, and AA (p<0.01)) at doses of 600 and 800mg of oral theophylline, Improvement persisted as long as treatment was continued (up to 72 months)
Phosphodiesterase Inhibitors	Lee et al. [556]	2022	Prospective, controlled	Intranasal theophylline irrigation (12 mg dissolved in 240 ml saline solution, ½ bottle as per day) (n=12); placebo (saline) (n=10) Duration: 6 weeks	Patients with PIOD; n=22	Change in SIT-40, Global Rating of Smell Change, QOD-NS, and ODOR after 6 weeks	No explicit p-values stated, but CI were overlapping for SIT-40: theophylline (10-38), placebo (8-39))	No clinically or statistically significant differences in treatment scores after 6 weeks, but a significant improvement in olfaction-related quality of life was observed in the treatment group
Phosphodiesterase Inhibitors	Meusel et al. [559]	2016	Experimental, placebo- controlled	Espresso with caffeine (65 mg/cup) (n=39); espresso without caffeine (placebo) (n=38)	Patients with sinonasal and PIOD n=76 48 PIOD 28 Sinonasal	Change in Sniffin' Sticks (TD) score 45 mins after espresso consumption; Subjective smell rating	No	The phosphodiesterase-inhibitor / adenosine-receptor agonist caffeine has little or no short-term effect on olfactory function
Intranasal Calcium Buffers	Philpott et al. [566]	2017	Prospective, controlled	Sodium citrate solution (0.5 ml in each nostril x 1 dose) (n=31); Placebo (sterile water, 0.5 ml in each nostril x 1 dose) (n=24)	Patients with olfactory dysfunction of mixed causes; n=55 21 PIOD 13 Idiopathic 4 PTOD	Change in phenyl ethyl alcohol, 1-butanol, eucalyptol, and acetic acid thresholds every 15 minutes up to a maximum of 2 hours	Yes (all odours except acetic acid, p<0.05)	Improved threshold scores in the treatment group compared to controls for 3 out of 4 odours tested, but effect is transient, peaking at 30-60 minutes after application, Rhinorrhoea and Sore throat were frequently reported side effects
Intranasal Calcium Buffers	Whitcroft et al. [684]	2017	Prospective, internally controlled	Intranasal sodium citrate (1 ml 3.5 g/ 140 ml, 10 to 15 drops in total BID in the left nostril); Placebo (1 ml saline, in the right nostril)	Patients with PIOD; n=49	Change in monorhinal Sniffin' Sticks (TI) score 20 to 30 minutes after treatment	Yes (composite TI: p=0.04)	Significant improvement in composite threshold and identification scores after treatment compared to placebo

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Intranasal Calcium Buffers	Whitcroft et al. [685]	2016	Prospective, controlled	Intranasal sodium citrate (1 ml 3.5 g/ 140 ml x 1 dose in the left or right nostril), Placebo (1 ml saline, in the contralateral nostril)	Patients with olfactory dysfunction of mixed causes; n=57 30 Sinonasal 10 PTOD 10 Idiopathic 7 PIOD	Change in monorhinal Sniffin' Sticks (TI) score 20 to 30 minutes after treatment	Yes (PIOD odour identification scores only, p=0.02)	Significantly improved identification scores in patients with post-infectious loss compared to placebo, No significant difference in threshold scores after treatment, Nasal discharge was the most common side effect
Intranasal Calcium Buffers	Whitcroft et al. [568]	2021	Prospective, internally controlled	Intranasal sodium citrate (1 ml 3.5 g/ 140 ml, 10 to 15 drops in total BID on the right nostril); No treatment (left nostril), Duration: 2 weeks	Patients with PIOD; n=60	Change in monorhinal Sniffin' Sticks (TDI) score after 2 weeks	No	No significant differences in TDI scores of treated and untreated sides, Statistically significant improvement in TDI scores before and after treatment (p<0.0001), Significant reduction in proportion of patients reporting phantosmia (p=0.001)
Intranasal Calcium Buffers	Panagiotopoulos et al. [564]	2005	Prospective	Sodium citrate buffer solution (3.5 g/140 ml x 1 dose) to the nasal cleft using head down and forwards position, Epinephrine (1 mg/ml, 1ml in each nostril x 1 dose), placebo (saline, 1ml in each nostril x 1 dose)	Patients with olfactory dysfunction of mixed causes; n=31 18 PIOD 7 Post-nasal surgery 5 Unspecified 1 PTOD	Change in Sniffin' Sticks 12-item screening test Day 1 olfaction evaluated 2 times (no medication and saline) Days 2 and 3 olfaction evaluated before and every 15 minutes after 1cc in each nostril of epinephrine (day 2) and sodium citrate buffer (day 3), for 1 hour	No	Significantly higher scores compared to baseline after administration of buffer solution (p<0.0001), Measured improvement in 97% of patients within one hour; 74% noticed improvement, with a median duration of 3 hours, Itching was the most common side effect
Novel Treatments	Hummel et al. [686]	2017	Retrospective cohort	Topical vitamin A (10,000 IU OD) + OT (n=124), OT only (n=46); Duration: 8 weeks	Patients with PIOD and PTOD; n=170 102 PIOD 68 PTOD	Change in Sniffin' Sticks (TDI) score after approximately 10 months	Yes (Odour discrimination higher for Vitamin A + OT for all patients, p=0.008; PIOD odour threshold and discrimination scores higher for Vitamin A + OT, p=0.01 and p=0.04 respectively	Vitamin A + OT group had significantly higher odour discrimination scores for all patients; and significantly higher threshold and discrimination scores in the post-infectious group
Novel Treatments	Reden et al. [631]	2012	Prospective, controlled	Oral vitamin A (10,000 IU OD x 3 months) (n=26) or placebo (n=26)	Patients with PIOD and PTOD; n=52 33 PIOD 19 PTOD	Change in Sniffin' Sticks (TDI) score after mean of 5 months	No	No significant difference between treatment and controls
Novel Treatments	Hernandez et al. [657]	2022	Prospective	Omega-3 (Omega 3 fatty acids 485 mg/capsule, 2 capsules BID) + OT (n=29) or OT only (n=29); Duration: 12 weeks	Patients with PIOD; n=58	Change in Sniffin' Sticks (TDI) score after 12 weeks	Yes (Odour threshold of Omega 3 + OT group, p=0.040)	Significantly higher score difference for threshold subtest among patients in the omega-3 group
Novel Treatments	Schöpf et al. [687]	2015	Prospective, controlled	Intranasal insulin (2 puffs in each nostril, 0.1 ml insulin / puff, total dose 0.4 ml = 40 IU) (n=10), placebo (saline, 2 puffs in each nostril, total dose 0.4ml) (n=7)	Patients with PIOD; n=10	Change in Sniffin' Sticks (TDI) score, subjective hedonic and intensity rating, (Insulin group: at baseline and 30 mins after treatment, with measurements 1 week apart; Placebo group: after mean of 55 weeks from insulin administration, before and after placebo, with measurements 1 week apart)	Yes (Subjective intensity rating, p=0.043)	No significant difference in TDI scores and subtests between measurements and groups, Improved odour threshold in 6 patients, Significant correlation between BMI, odour identification (r=0.909. p=0.005) and composite TDI (r=0.821, p=0.023) score after insulin administration
Novel Treatments	Reden et al. [688]	2011	Prospective, controlled	Minocycline (50 mg/ capsule, 2 capsules OD) (n=26); placebo (n=29); Duration: 21 days	Patients with PIOD; n=55	Change in Sniffin' Sticks (TDI) at mean of 207 days after initiation of treatment	No	Statistically, but not clinically significant increase in TDI scores for treatment (p=0.036) and control (p=0.009) groups, Spontaneous recovery in 20% of patients over a period of 7 months

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Novel Treatments	Quint et al. [689]	2002	Prospective, controlled	Caroverine (120 mg/day) (n=51), Control: zinc sulfate (400 mg/day) (n=26); Duration: 4 weeks	Patients with PIOD, PTOD, and idiopathic OD); n=77 38 PIOD 25 Idiopathic 14 PTOD	Change in Sniffin Sticks' (TDI) score, after 4 weeks	Unspecified	Significant improvement of odour thresholds among anosmics (p=0.005) and odour identification for all patients (Anosmia: p=0.038, Hyposmia: p=0.041), Zinc did not result in any significant measurable improvement in olfaction
Novel Treatments	Hummel et al. [612]	2002	Prospective	Oral alpha-lipoic acid (600 mg/day); Duration: 3 to 11 months, median of 4 months	Patients with PIOD; n=23	Change in Sniffin' Sticks (TDI) score, subjective parosmia questionnaire after treatment	No control group	Significant improvement of olfaction (p=0.002) after treatment; more pronounced in patients <60 years of age (p=0.018), Parosmia was less frequent after treatment (48% → 22%)
Novel Treatments	Seo et al. [512]	2009	Prospective, controlled	Oral prednisolone (30 mg/day x 3 days, 20 mg/day x 4 days, 10 mg/day x 7 days) + ginkgo biloba (80 mg TID) + intranasal mometasone furoate (2 puffs, BID x 4 weeks) (n=43); oral prednisolone + intranasal mometasone furoate(n=28); Duration: 4 weeks (Ginkgo biloba and intranasal mometasone), 2 weeks (Oral prednisolone)	Patients with PIOD; n=71	Butanol threshold test, CCSIT, after 4 weeks	No	No significant difference in improvement between corticosteroids + ginkgo biloba vs. controls (BSIT: p=0.66, CCSIT: p=0.08)
Sinonasal Olfactory Dysfunction								
Corticosteroids	Kim et al. [521]	2017	Retrospective, case series	Oral prednisolone (40 mg x 14 days, tapering by 5 mg daily) (n=60); intranasal mometasone furoate monohydrate spray (2 puffs, 100 µg in each nostril OD) (n=181); Oral prednisolone + intranasal mometasone spray (n=250); Duration: 16 days (Oral prednisolone), 1 month (Intranasal mometasone)	Patients with olfactory dysfunction of mixed causes; n=491 178 PIOD 96 PTOD 94 Sinonasal 89 Idiopathic 23 Previous Sinonasal Surgery 9 Xerostomia 2 Congenital	Change in CCCRCT, CCSIT, subjective rating (recovery vs. no recovery) 1 month after treatment	Yes (p<0.001)	Oral + intranasal and oral corticosteroid groups had better smell recovery outcomes than the intranasal group, No significant difference between oral + intranasal versus oral only (p<0.978)
Corticosteroids	Fleiner et al. [520]	2012	Retrospective	Topical corticosteroid (unspecified drug / dose) + OT (n=18); OT only (n=28); Duration: unspecified	Patients with olfactory dysfunction of mixed causes; n=46 16 PIOD 15 Sinonasal 8 Idiopathic 7 PTOD	Change in Sniffin' Sticks (TDI) scores at 4 or 8 months	Yes (p=0.001 at 8 months)	Statistically clinically significant improvement in TDI scores in the topical corticosteroid + OT group after 8 months of treatment
Corticosteroids	Heilmann et al. [519]	2004	Retrospective	Intranasal mometasone spray (2 sprays OD, ~0.1 mg per nostril) x 1 to 3 months) (n=37); oral prednisolone (40 mg/day, tapering doses over 21 days) (n=55); Duration: 1 to 3 months (Intranasal mometasone), 21 days (Oral prednisolone)	Patients with olfactory dysfunction of mixed causes; n=92 58 Idiopathic 22 PIOD 12 Sinonasal	Change in Sniffin' Sticks (TDI) scores after 21 to 330 days	Yes (p<0.001)	Treatment with oral prednisolone led to significantly improved TDI scores regardless of aetiology (p<0.001), intranasal mometasone had no significant effect on olfaction
Corticosteroids	Ikeda et al. [500]	1995	Non-controlled	Intranasal betamethasone (few drops of 0.1% solution to superior nasal cavity in Kaiteki position) (n=5) or beclomethasone dipropionate (aerosol, 400 mg/day) (n=16); then oral prednisolone (40 to 60 mg/day tapered over 10 to 14 days	Patients with PIOD; n=21 12 Sinonasal 9 PIOD	Change in T&T olfactometer threshold	Yes (Detection: p<0.05, Recognition: p<0.01 for sinonasal)	Significant improvement in T&T olfactometer detection and recognition thresholds for sinonasal group but not for post-infectious group

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Corticosteroids	Stenner et al. [509]	2008	Retrospective	Oral beclomethasone (3 to 0.5 mg OD to TID) + topical budesonide (1.5 mg/day, divided into 2 equal doses per side of the nose BID); oral beclomethasone + topical budesonide and neomycin (7.5 mg/day, divided into 2 equal doses per side of the nose BID); Duration: 20 days (Oral beclomethasone), 12 weeks (Topical budesonide only or with Neomycin)	Patients with olfactory dysfunction of mixed causes; n=89 31 PIOD 22 Idiopathic 16 Sinonasal 14 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after 12 weeks	No	No significant difference between TDI scores of treatment and control groups, Improved mean TDI scores with oral steroids across all treatment groups, with benefit from topical corticosteroids +/ antibiotic influenced by initial oral steroid responsiveness
Corticosteroids	Blomqvist et al. [518]	2003	Prospective, controlled	Oral prednisolone (40 mg/day x 3 days, tapering by 5 mg daily), then either Intranasal fluticasone spray (2 sprays, 100 µg OD in each nostril) (n=20); placebo spray (water, avisel, polysorbate 80, glucose, benzalkonium chloride (198 µg/g) and phenyl ethyl alcohol (2.5 mg/g) (n=10); no treatment (n=10); Duration: 10 days (Oral prednisolone), 6 months (Intranasal fluticasone, placebo)	Patients with olfactory dysfunction of mixed causes; n=40 23 PIOD 10 Sinonasal 7 Unknown/Idiopathic	Change in CC-CRCT, VAS after 10 days, 2, 6 months)	No	Significant improvement after the initial treatment with oral corticosteroids, no significant difference in olfactory threshold scores between treatment and control groups after 10 days, 2 and 6 months
Corticosteroids	Schriever et al. [510]	2012	Retrospective	Oral methyl-prednisolone (40 mg, then tapering by 5 mg every other day); Duration: 15 days	Patients with olfactory dysfunction of mixed causes; n=425 221 Sinonasal 157 Idiopathic 27 PIOD 20 PTOD, Post-surgical, Others)	Change in Sniffin' Sticks (TDI) scores after 15 days	No control group	Greater and clinically significant increase in TDI scores among patients with nasal polyps (p<0.001) who received treatment, PIOD (p=0.003) and idiopathic (p=0.01) patients who received corticosteroids also significantly improved but the improvement was less than those with sinonasal causes
Corticosteroids	Heilmann et al. [513]	2004	Prospective	Oral prednisolone (40 mg/day, tapering doses over 21 days) (n=85); intranasal mometasone (2 sprays OD in each nostril) (n=76); oral Vitamin B complex (thiamine 12 mg, riboflavin 12 mg, pyridoxine 0.75 mg, nicotinamide 60 mg, calcium pantothenate 6 mg 2 capsules TID) (n=31); Duration: 21 days (Oral prednisolone), 6 months (Intranasal mometasone and Vitamin B complex)	Patients with olfactory dysfunction of mixed causes; n=192 85 Idiopathic 72 PIOD 19 Sinonasal 10 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after an average of 2 and 6 months	No control group	Improvement following oral and intranasal corticosteroids (p<0.001, p=0.03 respectively); improvement with oral Vitamin B only after 6 months (p=0.001) but not after 2 months (p=0.07)
Monoclonal Antibodies	Barroso et al. [549]	2022	Retrospective	Omalizumab (n=81); Mepolizumab (n=65); Benralizumab (n=46); Reslizumab (n=14); Duration: minimum of 1 year	Patients with severe asthma and CRSwNP, n=206	Change in Subjective rating (Yes/No question on the degrees of smell loss: normosmia, hyposmia, anosmia)	Yes (Omalizumab: p=0.041)	No significant difference in total or partial improvement in loss of smell after treatment with any of the monoclonal antibodies, Significant increase in patients reporting normosmia in Omalizumab group compared to other monoclonal antibodies, Statistically significant decrease in subjects with anosmia from all groups except Reslizumab (p<0.0001)

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Monoclonal Antibodies	Mullol et al. [532]	2022	Prospective, controlled; Pooled analysis	SINUS-24: subcutaneous dupilumab (300mg SC every 2 weeks) + intranasal corticosteroids, placebo + intranasal corticosteroids; SINUS-52: dupilumab (every 2 weeks x 52 weeks), dupilumab (every 2 weeks x 24 weeks, then every 4 weeks until 52weeks), placebo every 2 weeks for 52 weeks Dupilumab (n=438), Placebo (n=286) Duration: 24 weeks (SINUS-24), 52 weeks (SINUS-52)	Patients with severe CRSwNP; n=724	Change in Subjective Loss of Smell (LoS) rating (0 to 3) daily, SIT-40 (at weeks 2, 8, 16, 24, 52), SNOT-22 (1 question, 0 to 5, at weeks 4, 8, 16, 24, 40, and 52)	Yes (LoS p<0.01, SIT-40 and SNOT-22 p<0.0001 at 2 and 8 weeks after)	Rapid and sustained improvement in olfactory function in the Dupilumab group compared to controls as early as week 2 until week 24 (SINUS-24, UPSIT, p<0.0001), Difference of 10.52 and 10.3 for weeks 24 and 52 respectively, between Dupilumab and placebo (SINUS-52, p<0.0001)
Monoclonal Antibodies	Oykhman et al. [546]	2022	Systematic review, network meta-analysis	Dupilumab; Omalizumab; Mepolizumab; Benralizumab; ASA-D	Patients with CRSwNP, 14 RCTs; n=2046	Change in SIT-40 score	Yes (Dupilumab [CI 9.75 to 12.17], Omalizumab [2.14 to 5.35], Mepolizumab [4.07 to 8.19], Benralizumab [1.02 to 4.88])	Moderate certainty evidence that Dupilumab > Omalizumab, Mepolizumab, Benralizumab, and ASA-D likely improves smell
Monoclonal Antibodies	Wu et al. [545]	2022	Systematic review, network meta-analysis	Dupilumab; Omalizumab; Mepolizumab; placebo	Patients with moderate to severe CRSwNP, 9 RCTs; n=1190	Change in SIT-40 score	Yes (p<0.00001 for Omalizumab or Dupilumab versus placebo (SIT-40))	Dupilumab had the best efficacy (WMD: 10.96) in terms of SIT-40 score; Omalizumab (WMD: 3.84) ranked second
Monoclonal Antibodies	Peters et al. [547]	2021	Systematic review, Indirect treatment comparison	Dupilumab; Omalizumab	Patients with CRSwNP, 4 RCTs; n=989	Change in SIT-40 score, Subjective Loss of Smell (LoS) rating (0 to 3)	Yes (LoS: MD -0.66 [95% CI -0.9 to -0.42]; SIT-40: MD 6.7 [95% CI 4.67 to 8.73])	Greater improvements in key CRSwNP outcomes with Dupilumab versus Omalizumab
Monoclonal Antibodies	Gevaert et al. [539]	2020	Prospective, controlled	Omalizumab (75 to 600 mg SC, every 2 or 4 weeks + intranasal mometasone (n=72 POLYP 1, 62 POLYP 2); placebo + intranasal mometasone (n=66 POLYP 1, 65 POLYP 2); Duration: 24 weeks	Patients with severe CRSwNP having inadequate INCS response; n=265	Change in SIT-40 score after weeks 4, 8, 16, and 24, Subjective Loss of Smell (LoS) score (0 to 3) daily	Yes (SIT-40: POLYP 1 p=0.0024, POLYP 2 p=0.011)	Improved SIT-40 scores in Omalizumab group vs. placebo, Significant difference in LoS score between Omalizumab and placebo only for POLYP 2.
Monoclonal Antibodies	Bachert et al. [531]	2019	Prospective, controlled	SINUS-24: Dupilumab (300 mg SC, every 2 weeks x 24 weeks) + intranasal mometasone furoate (2 sprays, 100 µg BID in each nostril) (n=143); placebo every 2 weeks for 24 weeks (n=133); SINUS-52: Dupilumab (300 mg SC every 2 weeks x 52 weeks) + intranasal mometasone furoate (n=150); Dupilumab (every 2 weeks x 24 weeks, then every 4 weeks until week 52 + intranasal mometasone furoate (n=145); placebo every 2 weeks x 52 weeks + intranasal mometasone furoate (n=153)	Patients with severe CRSwNP; n=276 (SINUS-24), 448 (SINUS-52)	Change in SIT-40 score after weeks 4, 8, 16, 24, 40, and 52), Subjective Loss of Smell (LoS) score (0 to 3) daily	Yes (SIT-40: p<0.0001 for SINUS-24 and -52; LoS: p<0.0001 for SINUS-24 and -52)	Significantly improved SIT-40 scores in the treatment groups compared with controls
Monoclonal Antibodies	Gevaert et al. [538]	2013	Prospective, controlled	Omalizumab (maximum 375 mg every 2 weeks total of 8 injections OR every month total of 4 injections) every 2 weeks x 20 weeks (n=15); placebo (n=8); Duration: 16 weeks	Patients with CRSwNP; n=23	Change in Subjective Loss of smell (LoS) score (0 to 3)	Yes LoS (p=0.004 after 16 weeks of treatment)	Significantly improved LoS scores in the Omalizumab group
Monoclonal Antibodies	Bachert et al. [544]	2022	Prospective, controlled	Benralizumab (30mg SC, every 4 weeks x 3 doses, then every 8 weeks) + Intranasal mometasone furoate spray (400 µg / day) (n=91); placebo + Intranasal mometasone furoate spray (n=91); Duration: 40 weeks	Patients with CRSwNP, history of systemic corticosteroid use and/or surgery, and symptomatic despite INCS; ¬n=413	Change in SIT-40, biweekly mean difficulty with sense of smell score (DSS) at week 40 and 56 (Self-rating from 0 to 3)	No (SIT-40) Yes (p=0.003 at week 40, p=0.002 at week 56 DSS)	Significantly improved DSS at week 40 and 56; no significant difference in SIT-40 scores between treatment and control groups at weeks 40 or 56

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Monoclonal Antibodies	Gevaert et al.[540]	2022	Prospective, open-label extension	Benralizumab (30mg SC, every 4 weeks x 3 doses, then every 8 weeks) + Intranasal mometasone furoate spray (400 µg / day) (n=91); placebo + Intranasal mometasone furoate spray (n=91); Duration: 40 weeks	Patients with CRSwNP, history of systemic corticosteroid use and/or surgery, and symptomatic despite INCS; ¬n=413	Change in SIT-40, biweekly mean difficulty with sense of smell score (DSS) at week 40 and 56 (Self-rating from 0 to 3)	No (SIT-40) Yes (p=0.003 at week 40, p=0.002 at week 56 DSS)	Significantly improved DSS at week 40 and 56; no significant difference in SIT-40 scores between treatment and control groups at weeks 40 or 56
Monoclonal Antibodies	Gevaert et al.[540]	2022	Prospective, controlled	Continued Omalizumab (75 to 600 mg SC every 2 or 4 weeks) + intranasal mometasone spray (400 µg or 200 µg daily if intolerant) x 28 weeks (n=123); Placebo then switched to Omalizumab (n=126) Duration: 52 weeks (continued Omalizumab), 28 weeks (placebo to Omalizumab)	Patients with CRSwNP who completed POLYP 1 or 2 (previous randomized placebo-controlled trials) n=249	Change in SIT-40 at 24 weeks after Omalizumab discontinuation	Unspecified	Patients who continued treatment experienced sustained improvement through 52 weeks, but gradually worsened over the 24-week follow up, but remained improved compared to pre-treatment levels
Monoclonal Antibodies	Han et al.[543]	2021	Prospective, controlled	Mepolizumab (100 mg IV every 4 weeks x 52 weeks) + intranasal mometasone furoate spray (2 sprays BID, 200 µg into each nostril daily) (n=206); placebo + intranasal mometasone furoate (n=201) Duration: 52 weeks (Mepolizumab), 56 weeks (Intranasal mometasone)	Patients with recurrent, refractory, severe, bilateral nasal polyp symptoms eligible for repeat nasal surgery; n=407	Change in SIT-40 score measured during alternating visits every 8 weeks), Subjective Loss of Smell (LoS) score (0 to 10, at week 49 to 52)	No (SIT-40) Yes (LoS, p=0.020)	Significant improvement in LoS scores; no significant difference in SIT-40 scores between groups (n=54 per treatment group, p=0.3)
Monoclonal Antibodies	Bachert et al. [541]	2017	Prospective, controlled	Intranasal fluticasone propionate (1 mg/ml, 2 sprays, 100 µg, OD in each nostril) + Mepolizumab (750 mg IV every 4 weeks x 6 doses) (n=42); intranasal fluticasone propionate + placebo (IV every 4 weeks x 6 doses (n=32) Duration: 21 weeks (Mepolizumab, placebo)	Patients with CRSwNP; n=74	Change in Sniffin' Sticks 12-item screening test score 4 weeks after last dose (at week 25); Subjective Loss of Smell (LoS) score (0 to 3)	No Sniffin' sticks 12-item screening test Yes (LoS score: p<0.05 at weeks 9 and 13, p<0.01 at week 21, p<0.0001 at week 25)	Significantly improved LoS scores after 25 weeks of Mepolizumab
Monoclonal Antibodies	Gevaert et al.[542]	2011	Prospective, controlled	Mepolizumab (750mg IV x 2 doses) (n=20); placebo (n=10)	Patients with severe nasal polyposis (grade 3 or 4 or recurrent after surgery) refractory to corticosteroid therapy; n=30	Change in Subjective Loss of Smell (LoS) score (0 to 3)	No	Long-lasting improvement (until 11 months after last dose) in subjective LoS scores after treatment with Mepolizumab, but did not reach statistical significance
Monoclonal Antibodies	Pinto et al. [537]	2010	Prospective, controlled	Omalizumab (0.016 mg/kg per IU total serum IgE/ml SC every 2 or 4 weeks) (n=7); placebo (n=7); Duration: 6 months	Patients with treatment-refractory CRS; n=14	Change in SIT-40 score after 6 months, subjective hyposmia symptoms (0 to 3) daily	No	No significant improvement in SIT-40 scores in the treatment group vs controls (p<0.31)
Phosphodiesterase Inhibitors	Hosein & Henkin [551]	2022	Prospective	Intranasal theophylline (20 µg in 0.4 ml saline solution, 1 spray OD, with increasing dosage if no improvement after 2-4 months after to a maximum of 4 sprays / day) (n=39), placebo (saline) (n=39), normal (n=17) Duration: at least 2 months	Patients with normal olfactory function and hyposmia from multiple causes; n=56 12 PIOD 9 PTOD 7 Sinonasal 5 Idiopathic 3 Chemical Exposure 3 Congenital	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)) after at least 2 months of treatment	Yes (DT: all odours, p<0.01, RT: PYR p<0.005, NO2B, THIO, AA p<0.01)	Over half of treated patients experienced a decrease in nasal mucus IL-10 toward control levels after intranasal theophylline administration, correlated with a significant improvement in taste and smell function
Phosphodiesterase Inhibitors	Henkin et al. [554]	2012	Prospective, internally controlled	Oral theophylline anhydrous (200 to 800 mg/day x 2 to 12 months; intranasal theophylline methylpropyl paraben 20 µg/day in each naris x 4 weeks, controls were same group	Patients with olfactory dysfunction of mixed causes; n=10 3 Sinonasal 3 PIOD 2 PTOD 1 Congenital 1 Other	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100)	Yes (DT for Sucrose and Hydrochloride (p<0.01), and Urea, (p<0.05))	Intranasal theophylline treatment improved taste and smell acuity in 8 of 10 patients after 4 weeks, Oral theophylline treatment improved taste and smell acuity in 6 of 10 patients after 2-12 months

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Phosphodiesterase Inhibitors	Henkin et al. [550]	2017	Prospective	Oral theophylline (200 to 800 mg taken over 2 to 10 months) (n=44)	Patients with hyposmia from multiple causes; n=44 10 PIOD 15 Sinonasal 9 Congenital 8 PTOD 1 Post-anaesthesia 1 Oropyrosis/Dysgeusia	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective improvement in smell/taste/flavour (0 to 100)	No control group	Significant improvement in subjective responses in smell (p<0.05), taste, and flavour perception and in olfactometry, associated with increased nasal mucus sonic hedgehog and serum theophylline after treatment
Phosphodiesterase Inhibitors	Henkin et al. [553]	2009	Prospective	Oral Theophylline in increasing doses (200, 400, 600, and 800 mg) over 2-8 months	Patients with olfactory dysfunction of mixed causes; n=312 97 PIOD 97 Sinonasal 76 Others 42 PTOD	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100) daily	No control group	Subjective smell loss improved in 157 patients (50.3%), Greater improvement in mean DT and RT before and after treatment (DT: PYR (p<0.001), NO2B (p<0.05), THIO and AA (p<0.01); RT: PYRD and NO2B (p<0.001), NO2B THIO and AA (p<0.01)) at doses of 600 and 800mg of oral theophylline, Improvement persisted as long as treatment was continued (up to 72 months)
Phosphodiesterase Inhibitors	Meusel et al. [559]	2016	Experimental, placebo- controlled	Espresso with caffeine (65 mg/cup) (n=39); espresso without caffeine (placebo) (n=38)	Patients with sinonasal or PIOD; n=76 48 PIOD 28 Sinonasal	Change in Sniffin' Sticks (TD) score 45 mins after espresso consumption; Subjective smell rating	No	The phosphodiesterase-inhibitor / adenosine-receptor agonist caffeine has little or no short-term effect on olfactory function
Intranasal Calcium Buffers	Whitcroft et al. [685]	2016	Prospective, controlled	Intranasal sodium citrate (1 ml 3.5 g/ 140 ml x 1 dose in the left or right nostril), Placebo (1 ml saline, in the contralateral nostril)	Patients with olfactory dysfunction of mixed causes; n=57 30 Sinonasal 10 Idiopathic 10 PTOD 7 PIOD	Change in monorhinal Sniffin' Sticks (TI) score 20 to 30 minutes after treatment	Yes (PIOD odour identification scores only, p=0.02)	Significantly improved identification scores in patients with post-infectious loss compared to placebo, No significant difference in threshold scores after treatment, Nasal discharge was the most common side effect
Post-traumatic Olfactory Dysfunction								
Corticosteroids	Kim et al. [521]	2017	Retrospective, case series	Oral prednisolone (40 mg x 14 days, tapering by 5 mg daily) (n=60); intranasal mometasone furoate monohydrate spray (2 puffs, 100 µg in each nostril OD) (n=181); Oral prednisolone + intranasal mometasone spray (n=250) Duration: 16 days (Oral prednisolone), 1 month (Intranasal mometasone)	Patients with olfactory dysfunction of mixed causes; n=491 178 PIOD 96 PTOD 94 Sinonasal 89 Idiopathic 23 Previous Sinonasal Surgery 9 Xerostomia 2 Congenital	Change in CCCRCT, CCSIT, subjective rating (recovery vs. no recovery) 1 month after treatment	Yes (p<0.001)	Oral + intranasal and oral corticosteroid groups had better smell recovery outcomes than the intranasal group, No significant difference between oral + intranasal versus oral only (p<0.978)
Corticosteroids	Fleiner et al. [520]	2012	Retrospective	Topical corticosteroid (unspecified drug / dose) + OT (n=18); OT only (n=28) Duration: unspecified	Patients with olfactory dysfunction of mixed causes; n=46 16 PIOD 15 Sinonasal 8 Idiopathic 7 PTOD	Change in Sniffin' Sticks (TDI) scores at 4 or 8 months	Yes (p=0.001 at 8 months)	Statistically clinically significant improvement in TDI scores in the topical corticosteroid + OT group after 8 months of treatment
Corticosteroids	Nguyen & Patel [522]	2018	Prospective, controlled	Intranasal budesonide irrigation (0.5 mg/ 2 ml BID) + OT (n=66); Intranasal saline irrigation (BID) + OT (n=67) Duration: 6 months	Patients with olfactory dysfunction of mixed causes; n=133 62 PIOD 46 Idiopathic 16 PTOD 6 Medication-related 3 Environmental exposure	Clinically significant change in SIT-40 after 6 months	No	Clinically significant change in SIT-40 scores in 35.3% of patients (n=47), Younger age and shorter duration of OD were associated with improvement (p<0.0001)

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Corticosteroids	Stenner et al. [509]	2008	Retrospective	Oral beclomethasone (3 to 0.5 mg OD to TID) + topical budesonide (1.5 mg/day, divided into 2 equal doses per side of the nose BID); oral beclomethasone + topical budesonide and neomycin (7.5 mg/day, divided into 2 equal doses per side of the nose BID) Duration: 20 days (Oral beclomethasone), 12 weeks (Topical budesonide only or with Neomycin)	Patients with olfactory dysfunction of mixed causes; n=89 31 PIOD 22 Idiopathic 16 Sinonasal 14 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after 12 weeks	No	No significant difference between TDI scores of treatment and control groups, Improved mean TDI scores with oral steroids across all treatment groups, with benefit from topical corticosteroids +/ antibiotic influenced by initial oral steroid responsiveness
Corticosteroids	Bratt et al [507]	2020	Prospective	Oral prednisolone (30 mg OD), then OT only Duration: 10 days (Oral prednisolone); 3 months (OT)	Patients with PTOD; n=22	Change in Sniffin' Sticks (TDI) score after 10 days, 3, and 12 months	No control group	Clinically significant (≥6) improvement in composite threshold, discrimination, and identification score in 50% of participants after 1 year (p<0.001)
Corticosteroids	Jiang et al. [690]	2010	Prospective	Oral prednisolone (15 mg QID x 3 days, then 10 mg QID x 3 days, 10 mg TID x 3 days, tapering by 10 mg/day every 3 days) Duration: 15 days	Patients with PTOD; n=116	Change in PEA threshold test (monthly for 3 months after treatment)	No control group	Improvement in only 16.4% of patients; spontaneous recovery cannot be ruled out, Patients whose thresholds improved were significantly younger (p=0.033)
Corticosteroids	Heilmann et al. [513]	2004	Prospective	Oral prednisolone (40 mg/day, tapering doses over 21 days) (n=85); intranasal mometasone (2 sprays OD in each nostril) (n=76); oral Vitamin B complex (thiamine 12 mg, riboflavin 12 mg, pyridoxine 0.75 mg, nicotinamide 60 mg, calcium pantothenate 6 mg 2 capsules TID) (n=31) Duration: 21 days (Oral prednisolone), 6 months (Intranasal mometasone and Vitamin B complex)	Patients with olfactory dysfunction of mixed causes; n=192 85 Idiopathic 72 PIOD 19 Sinonasal 10 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after an average of 2 and 6 months	No control group	Improvement following oral and intranasal corticosteroids (p<0.001, p=0.03 respectively); improvement with oral Vitamin B only after 6 months (p=0.001) but not after 2 months (p=0.07)
Corticosteroids	Fujii et al. [505]	2002	Prospective	Dexamethasone septal injection (4 mg/0.5 ml every 2 weeks x 8 times)	Patients with PTOD; n=27	Change in T&T olfactometer threshold, Alinamin test score after 4 months	No control group	Improvement of detection thresholds in 6 patients, improvement of recognition thresholds in 4 patients
Phosphodiesterase Inhibitors	Hosein & Henkin [551]	2022	Prospective	Intranasal theophylline (20 µg in 0.4 ml saline solution, 1 spray OD, with increasing dosage if no improvement after 2-4 months after to a maximum of 4 sprays / day) (n=39), placebo (saline) (n=39), normal (n=17) Duration: at least 2 months	Patients with normal olfactory function and hyposmia from multiple causes; n=56 12 PIOD 9 PTOD 7 Sinonasal 5 Idiopathic 3 Chemical Exposure 3 Congenital	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)) after at least 2 months of treatment	Yes (DT: all odours, p<0.01, RT: PYR p<0.005, NO2B, THIO, AA p<0.01)	Over half of treated patients experienced a decrease in nasal mucus IL-10 toward control levels after intranasal theophylline administration, correlated with a significant improvement in taste and smell function
Phosphodiesterase Inhibitors	Henkin et al. [554]	2012	Prospective, internally controlled	Oral theophylline anhydrous (200 to 800 mg/day x 2 to 12 months; intranasal theophylline methylpropyl paraben 20 µg/day in each naris x 4 weeks, controls were same group	Patients with olfactory dysfunction of mixed causes; n=10 3 Sinonasal 3 PIOD 2 PTOD 1 Congenital 1 Other	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100)	Yes (DT for Sucrose and Hydrochloride (p<0.01), and Urea, (p<0.05))	Intranasal theophylline treatment improved taste and smell acuity in 8 of 10 patients after 4 weeks, Oral theophylline treatment improved taste and smell acuity in 6 of 10 patients after 2-12 months

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Phosphodiesterase Inhibitors	Henkin et al. [550]	2017	Prospective	Oral theophylline (200 to 800 mg taken over 2 to 10 months) (n=44)	Patients with hyposmia from multiple causes; n=44 10 PIOD 15 Sinonasal 9 Congenital 8 PTOD 1 Post-anaesthesia 1 Oropyrosis/Dysgeusia	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective improvement in smell/taste/flavour (0 to 100)	No control group	Significant improvement in subjective responses in smell (p<0.05), taste, and flavour perception and in olfactometry, associated with increased nasal mucus sonic hedgehog and serum theophylline after treatment
Phosphodiesterase Inhibitors	Henkin et al. [553]	2009	Prospective	Oral Theophylline in increasing doses (200, 400, 600, and 800 mg) over 2-8 months	Patients with olfactory dysfunction of mixed causes; n=312 97 PIOD 97 Sinonasal 76 Others 42 PTOD	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100) daily	No control group	Subjective smell loss improved in 157 patients (50.3%), Greater improvement in mean DT and RT before and after treatment (DT: PYR (p<0.001), NO2B (p<0.05), THIO and AA (p<0.01); RT: PYRD and NO2B (p<0.001), NO2B THIO and AA (p<0.01)) at doses of 600 and 800mg of oral theophylline, Improvement persisted as long as treatment was continued (up to 72 months)
Intranasal Calcium Buffers	Philpott et al. [566]	2017	Prospective, controlled	Sodium citrate solution (0.5 ml in each nostril x 1 dose) (n=31); Placebo (sterile water, 0.5 ml in each nostril x 1 dose) (n=24)	Patients with olfactory dysfunction of mixed causes; n=55 21 PIOD 13 Idiopathic 4 PTOD	Change in phenyl ethyl alcohol, 1-butanol, eucalyptol, and acetic acid thresholds every 15 minutes up to a maximum of 2 hours	Yes (all odours except acetic acid, p<0.05)	Improved threshold scores in the treatment group compared to controls for 3 out of 4 odours tested, but effect is transient, peaking at 30-60 minutes after application, Rhinorrhoea and Sore throat were frequently reported side effects
Intranasal Calcium Buffers	Panagiotopoulos et al. [564]	2005	Prospective	Sodium citrate buffer solution (3.5 g/140 ml x 1 dose) to the nasal cleft using head down and forwards position, Epinephrine (1 mg/ml, 1ml in each nostril x 1 dose), placebo (saline, 1ml in each nostril x 1 dose)	Patients with olfactory dysfunction of mixed causes; n=31 18 PIOD 7 Post-nasal surgery 1 PTOD 5 Unspecified	Change in Sniffin' Sticks 12-item screening test Day 1 olfaction evaluated 2 times (no medication and saline) Days 2 and 3 olfaction evaluated before and every 15 minutes after 1cc in each nostril of epinephrine (day 2) and sodium citrate buffer (day 3), for 1 hour	No	Significantly higher scores compared to baseline after administration of buffer solution (p<0.0001), Measured improvement in 97% of patients within one hour; 74% noticed improvement, with a median duration of 3 hours, Itching was the most common side effect
Intranasal Calcium Buffers	Whitcroft et al. [685]	2016	Prospective, controlled	Intranasal sodium citrate (1 ml 3.5 g/ 140 ml x 1 dose in the left or right nostril), Placebo (1 ml saline, in the contralateral nostril)	Patients with olfactory dysfunction of mixed causes; n=57 30 Sinonasal 10 Idiopathic 10 PTOD 7 PIOD	Change in monorhinal Sniffin' Sticks (TI) score 20 to 30 minutes after treatment	Yes (PIOD odour identification scores only, p=0.02)	Significantly improved identification scores in patients with post-infectious loss compared to placebo, No significant difference in threshold scores after treatment, Nasal discharge was the most common side effect
Zinc	Jiang et al. [511]	2015	Prospective, controlled	Zinc gluconate (10 mg TID x 1 month) + prednisolone (1 mg/kg/day then tapering for 2 weeks) (n=39); zinc only (10 mg TID x 1 month) (n=35); prednisolone only (n=34); no treatment (n=37)	Patients with post-traumatic anosmia; n=145	Change in Phenyl ethyl alcohol odour detection threshold test monthly up to a mean of 5 to 6 months after, MRI for OB measurement 2 months after treatment	Yes (recovery rates: p=0.006 for zinc + prednisolone, p=0.013 for zinc only)	Zinc + steroid application and zinc only groups showed significant threshold improvement compared to "no treatment"
Novel Treatments	Hummel et al. [686]	2017	Retrospective cohort	Topical vitamin A (10,000 IU OD) + OT (n=124), OT only (n=46) Duration: 8 weeks	Patients with PIOD and PTOD; n=170 102 PIOD 68 PTOD	Change in Sniffin' Sticks (TDI) score after approximately 10 months	Yes (Odour discrimination higher for Vitamin A + OT for all patients, p=0.008; PIOD odour threshold and discrimination scores higher for Vitamin A + OT, p=0.01 and p=0.04 respectively	Vitamin A + OT group had significantly higher odour discrimination scores for all patients; and significantly higher threshold and discrimination scores in the post-infectious group

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Novel Treatments	Reden et al. [631]	2012	Prospective, controlled	Oral vitamin A (10,000 IU OD x 3 months) (n=26) or placebo (n=26)	Patients with PIOD and PTOD; n=52 33 PIOD 19 PTOD	Change in Sniffin' Sticks (TDI) score after mean of 5 months	No	No significant difference between treatment and controls
Novel Treatments	Quint et al. [689]	2002	Prospective, controlled	Caroverine (120 mg/day) (n=51), Control: zinc sulfate (400 mg/day) (n=26) Duration: 4 weeks	Patients with olfactory dysfunction of mixed causes; n=77 38 PIOD 25 Idiopathic 14 PTOD	Change in Sniffin Sticks' (TDI) score, after 4 weeks	Unspecified	Significant improvement of odour thresholds among anosmics (p=0.005) and odour identification for all patients (Anosmia: p=0.038, Hyposmia: p=0.041), Zinc did not result in any significant measurable improvement in olfaction
				Idiopathic Olfactory Dysfunction				
Corticosteroids	Kim et al. [521]	2017	Retrospective, case series	Oral prednisolone (40 mg x 14 days, tapering by 5 mg daily) (n=60); intranasal mometasone furoate monohydrate spray (2 puffs, 100 µg in each nostril OD) (n=181); Oral prednisolone + intranasal mometasone spray (n=250) Duration: 16 days (Oral prednisolone), 1 month (Intranasal mometasone)	Patients with olfactory dysfunction of mixed causes; n=491 178 PIOD 96 PTOD 94 Sinonasal 89 Idiopathic 23 Previous Sinonasal Surgery 9 Xerostomia 2 Congenital	Change in CCCRCT, CCSIT, subjective rating (recovery vs. no recovery) 1 month after treatment	Yes (p<0.001)	Oral + intranasal and oral corticosteroid groups had better smell recovery outcomes than the intranasal group, No significant difference between oral + intranasal versus oral only (p<0.978)
Corticosteroids	Fleiner et al. [520]	2012	Retrospective	Topical corticosteroid (unspecified drug / dose) + OT (n=18); OT only (n=28) Duration: unspecified	Patients with olfactory dysfunction of mixed causes; n=46 16 PIOD 15 Sinonasal 8 Idiopathic 7 PTOD	Change in Sniffin' Sticks (TDI) scores at 4 or 8 months	Yes (p=0.001 at 8 months)	Statistically clinically significant improvement in TDI scores in the topical corticosteroid + OT group after 8 months of treatment
Corticosteroids	Heilmann et al. [519]	2004	Retrospective	Intranasal mometasone spray (2 sprays OD, ~0.1 mg per nostril) x 1 to 3 months) (n=37); oral prednisolone (40 mg/day, tapering doses over 21 days) (n=55) Duration: 1 to 3 months (Intranasal mometasone), 21 days (Oral prednisolone)	Patients with olfactory dysfunction of mixed causes; n=92 58 Idiopathic 22 PIOD 12 Sinonasal	Change in Sniffin' Sticks (TDI) scores after 21 to 330 days	Yes (p<0.001)	Treatment with oral prednisolone led to significantly improved TDI scores regardless of aetiology (p<0.001), intranasal mometasone had no significant effect on olfaction
Corticosteroids	Nguyen & Patel [522]	2018	Prospective, controlled	Intranasal budesonide irrigation (0.5 mg/ 2 ml BID) + OT (n=66); Intranasal saline irrigation (BID) + OT (n=67) Duration: 6 months	Patients with olfactory dysfunction of mixed causes; n=133 62 PIOD 46 Idiopathic 16 PTOD 6 Medication-related 3 Environmental exposure	Clinically significant change in SIT-40 after 6 months	No	Clinically significant change in SIT-40 scores in 35.3% of patients (n=47), Younger age and shorter duration of OD were associated with improvement (p<0.0001)
Corticosteroids	Stenner et al. [509]	2008	Retrospective	Oral beclomethasone (3 to 0.5 mg OD to TID) + topical budesonide (1.5 mg/day, divided into 2 equal doses per side of the nose BID); oral beclomethasone + topical budesonide and neomycin (7.5 mg/day, divided into 2 equal doses per side of the nose BID) Duration: 20 days (Oral beclomethasone), 12 weeks (Topical budesonide only or with Neomycin)	Patients with olfactory dysfunction of mixed causes; n=89 31 PIOD 22 Idiopathic 16 Sinonasal 14 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after 12 weeks	No	No significant difference between TDI scores of treatment and control groups, Improved mean TDI scores with oral steroids across all treatment groups, with benefit from topical corticosteroids +/- antibiotic influenced by initial oral steroid responsiveness

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Corticosteroids	Blomqvist et al. [518]	2003	Prospective, controlled	Oral prednisolone (40 mg/day x 3 days, tapering by 5 mg daily), then either Intranasal fluticasone spray (2 sprays, 100 µg OD in each nostril) (n=20); placebo spray (water, avisel, polysorbate 80, glucose, benzalkonium chloride (198 µg/g) and phenyl ethyl alcohol (2.5 mg/g) (n=10); no treatment (n=10) Duration: 10 days (Oral prednisolone), 6 months (Intranasal fluticasone, placebo)	Patients with olfactory dysfunction of mixed causes; n=40 23 PIOD 10 Sinonasal 7 Unknown/Idiopathic	Change in CC-CRCT, VAS after 10 days, 2, 6 months)	No	Significant improvement after the initial treatment with oral corticosteroids, no significant difference in olfactory threshold scores between treatment and control groups after 10 days, 2 and 6 months
Corticosteroids	Schriever et al. [510]	2012	Retrospective	Oral methyl-prednisolone (40 mg, then tapering by 5 mg every other day) Duration: 15 days	Patients with olfactory dysfunction of mixed causes; n=425 221 Sinonasal 157 Idiopathic 27 PIOD 20 PTOD, Post-surgical, Others)	Change in Sniffin' Sticks (TDI) scores after 15 days	No control group	Greater and clinically significant increase in TDI scores among patients with nasal polyps (p<0.001) who received treatment, PIOD (p=0.003) and idiopathic (p=0.01) patients who received corticosteroids also significantly improved but the improvement was less than those with sinonasal causes
Corticosteroids	Heilmann et al. [513]	2004	Prospective	Oral prednisolone (40 mg/day, tapering doses over 21 days) (n=85); intranasal mometasone (2 sprays OD in each nostril) (n=76); oral Vitamin B complex (thiamine 12 mg, riboflavin 12 mg, pyridoxine 0.75 mg, nicotinamide 60 mg, calcium pantothenate 6 mg 2 capsules TID) (n=31); Duration: 21 days (Oral prednisolone), 6 months (Intranasal mometasone and Vitamin B complex)	Patients with olfactory dysfunction of mixed causes; n=192 85 Idiopathic 72 PIOD 19 Sinonasal 10 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after an average of 2 and 6 months	No control group	Improvement following oral and intranasal corticosteroids (p<0.001, p=0.03 respectively); improvement with oral Vitamin B only after 6 months (p=0.001) but not after 2 months (p=0.07)
Monoclonal Antibodies	Barroso et al.[549]	2022	Retrospective	Omalizumab (n=81); Mepolizumab (n=65); Benralizumab (n=46); Reslizumab (n=14); Duration: minimum of 1 year	Patients with severe asthma and CRSwNP, n=206	Change in Subjective rating (Yes/No question on the degrees of smell loss: normosmia, hyposmia, anosmia)	Yes (Omalizumab: p=0.041)	No significant difference in total or partial improvement in loss of smell after treatment with any of the monoclonal antibodies, Significant increase in patients reporting normosmia in Omalizumab group compared to other monoclonal antibodies, Statistically significant decrease in subjects with anosmia from all groups except Reslizumab (p<0.0001)
Monoclonal Antibodies	Mullol et al. [532]	2022	Prospective, controlled; Pooled analysis	SINUS-24: subcutaneous dupilumab (300mg SC every 2 weeks) + intranasal corticosteroids, placebo + intranasal corticosteroids; SINUS-52: dupilumab (every 2 weeks x 52 weeks), dupilumab (every 2 weeks x 24 weeks, then every 4 weeks until 52weeks), placebo every 2 weeks for 52 weeks Dupilumab (n=438), Placebo (n=286) Duration: 24 weeks (SINUS-24), 52 weeks (SINUS-52)	Patients with severe CRSwNP; n=724	Change in Subjective Loss of Smell (LoS) rating (0 to 3) daily, SIT-40 (at weeks 2, 8, 16, 24, 52), SNOT-22 (1 question, 0 to 5, at weeks 4, 8, 16, 24, 40, and 52)	Yes (LoS p<0.01, SIT-40 and SNOT-22 p<0.0001 at 2 and 8 weeks after)	Rapid and sustained improvement in olfactory function in the Dupilumab group compared to controls as early as week 2 until week 24 (SINUS-24, UPSIT, p<0.0001), Difference of 10.52 and 10.3 for weeks 24 and 52 respectively, between Dupilumab and placebo (SINUS-52, p<0.0001)
Monoclonal Antibodies	Oykhman et al.[546]	2022	Systematic review, network meta-analysis	Dupilumab; Omalizumab; Mepolizumab; Benralizumab; ASA-D	Patients with CRSwNP, 14 RCTs; n=2046	Change in SIT-40 score	Yes (Dupilumab [CI 9.75 to 12.17], Omalizumab [2.14 to 5.35], Mepolizumab [4.07 to 8.19], Benralizumab [1.02 to 4.88])	Moderate certainty evidence that Dupilumab > Omalizumab, Mepolizumab, Benralizumab, and ASA-D likely improves smell

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Monoclonal Antibodies	Wu et al.[545]	2022	Systematic review, network meta-analysis	Dupilumab; Omalizumab; Mepolizumab; placebo	Patients with moderate to severe CRSwNP, 9 RCTs; n=1190	Change in SIT-40 score	Yes (p<0.00001 for Omalizumab or Dupilumab versus placebo (SIT-40))	Dupilumab had the best efficacy (WMD: 10.96) in terms of SIT-40 score; Omalizumab (WMD: 3.84) ranked second
Monoclonal Antibodies	Peters et al. [547]	2021	Systematic review, Indirect treatment comparison	Dupilumab; Omalizumab	Patients with CRSwNP, 4 RCTs; n=989	Change in SIT-40 score, Subjective Loss of Smell (LoS) rating (0 to 3)	Yes (LoS: MD -0.66 [95% CI -0.9 to -0.42]; SIT-40: MD 6.7 [95% CI 4.67 to 8.73])	Greater improvements in key CRSwNP outcomes with Dupilumab versus Omalizumab
Monoclonal Antibodies	Gevaert et al.[539]	2020	Prospective, controlled	Omalizumab (75 to 600 mg SC, every 2 or 4 weeks + intranasal mometasone (n=72 POLYP 1, 62 POLYP 2); placebo + intranasal mometasone (n=66 POLYP 1, 65 POLYP 2); Duration: 24 weeks	Patients with severe CRSwNP having inadequate INCS response; n=265	Change in SIT-40 score after weeks 4, 8, 16, and 24, Subjective Loss of Smell (LoS) score (0 to 3) daily	Yes (SIT-40: POLYP 1 p=0.0024, POLYP 2 p=0.011)	Improved SIT-40 scores in Omalizumab group vs. placebo, Significant difference in LoS score between Omalizumab and placebo only for POLYP 2.
Monoclonal Antibodies	Bachert et al. [531]	2019	Prospective, controlled	SINUS-24: Dupilumab (300 mg SC, every 2 weeks x 24 weeks) + intranasal mometasone furoate (2 sprays, 100 µg BID in each nostril) (n=143); placebo every 2 weeks for 24 weeks (n=133); SINUS-52: Dupilumab (300 mg SC every 2 weeks x 52 weeks) + intranasal mometasone furoate (n=150); Dupilumab (every 2 weeks x 24 weeks, then every 4 weeks until week 52 + intranasal mometasone furoate (n=145); placebo every 2 weeks x 52 weeks + intranasal mometasone furoate (n=153)	Patients with severe CRSwNP; n=276 (SINUS-24), 448 (SINUS-52)	Change in SIT-40 score after weeks 4, 8, 16, 24, 40, and 52), Subjective Loss of Smell (LoS) score (0 to 3) daily	Yes (SIT-40: p<0.0001 for SINUS-24 and -52; LoS: p<0.0001 for SINUS-24 and -52)	Significantly improved SIT-40 scores in the treatment groups compared with controls
Monoclonal Antibodies	Gevaert et al. [538]	2013	Prospective, controlled	Omalizumab (maximum 375 mg every 2 weeks total of 8 injections OR every month total of 4 injections) every 2 weeks x 20 weeks (n=15); placebo (n=8); Duration: 16 weeks	Patients with CRSwNP; n=23	Change in Subjective Loss of smell (LoS) score (0 to 3)	Yes LoS (p=0.004 after 16 weeks of treatment)	Significantly improved LoS scores in the Omalizumab group
Monoclonal Antibodies	Bachert et al. [544]	2022	Prospective, controlled	Benralizumab (30mg SC, every 4 weeks x 3 doses, then every 8 weeks) + Intranasal mometasone furoate spray (400 µg / day) (n=91); placebo + Intranasal mometasone furoate spray (n=91); Duration: 40 weeks	Patients with CRSwNP, history of systemic corticosteroid use and/or surgery, and symptomatic despite INCS; ¬n=413	Change in SIT-40, biweekly mean difficulty with sense of smell score (DSS) at week 40 and 56 (Self-rating from 0 to 3)	No (SIT-40) Yes (p=0.003 at week 40, p=0.002 at week 56 DSS)	Significantly improved DSS at week 40 and 56; no significant difference in SIT-40 scores between treatment and control groups at weeks 40 or 56
Monoclonal Antibodies	Gevaert et al.[540]	2022	Prospective, open-label extension	Continued Omalizumab (75 to 600 mg SC every 2 or 4 weeks) + intranasal mometasone spray (400 µg or 200 µg daily if intolerant) x 28 weeks (n=123); Placebo then switched to Omalizumab (n=126) Duration: 52 weeks (continued Omalizumab), 28 weeks (placebo to Omalizumab)	Patients with CRSwNP who completed POLYP 1 or 2 (previous randomized placebo-controlled trials) n=249	Change in SIT-40 at 24 weeks after Omalizumab discontinuation	Unspecified	Patients who continued treatment experienced sustained improvement through 52 weeks, but gradually worsened over the 24-week follow up, but remained improved compared to pre-treatment levels
Monoclonal Antibodies	Han et al.[543]	2021	Prospective, controlled	Mepolizumab (100 mg IV every 4 weeks x 52 weeks) + intranasal mometasone furoate spray (2 sprays BID, 200 µg into each nostril daily) (n=206); placebo + intranasal mometasone furoate (n=201) Duration: 52 weeks (Mepolizumab), 56 weeks (Intranasal mometasone)	Patients with recurrent, refractory, severe, bilateral nasal polyp symptoms eligible for repeat nasal surgery; n=407	Change in SIT-40 score measured during alternating visits every 8 weeks), Subjective Loss of Smell (LoS) score (0 to 10, at week 49 to 52)	No (SIT-40) Yes (LoS, p=0.020)	Significant improvement in LoS scores; no significant difference in SIT-40 scores between groups (n=54 per treatment group, p=0.3)

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Monoclonal Antibodies	Bachert et al. [541]	2017	Prospective, controlled	Intranasal fluticasone propionate (1 mg/ml, 2 sprays, 100 µg, OD in each nostril) + Mepolizumab (750 mg IV every 4 weeks x 6 doses) (n=42); intranasal fluticasone propionate + placebo (IV every 4 weeks x 6 doses (n=32) Duration: 21 weeks (Mepolizumab, placebo)	Patients with CRSwNP; n=74	Change in Sniffin' Sticks 12-item screening test score 4 weeks after last dose (at week 25); Subjective Loss of Smell (LoS) score (0 to 3)	No Sniffin' sticks 12-item screening test Yes (LoS score: p<0.05 at weeks 9 and 13, p<0.01 at week 21, p<0.0001 at week 25)	Significantly improved LoS scores after 25 weeks of Mepolizumab
Monoclonal Antibodies	Gevaert et al.[542]	2011	Prospective, controlled	Mepolizumab (750mg IV x 2 doses) (n=20); placebo (n=10)	Patients with severe nasal polyposis (grade 3 or 4 or recurrent after surgery) refractory to corticosteroid therapy; n=30	Change in Subjective Loss of Smell (LoS) score (0 to 3)	No	Long-lasting improvement (until 11 months after last dose) in subjective LoS scores after treatment with Mepolizumab, but did not reach statistical significance
Monoclonal Antibodies	Pinto et al. [537]	2010	Prospective, controlled	Omalizumab (0.016 mg/kg per IU total serum IgE/ml SC every 2 or 4 weeks) (n=7); placebo (n=7); Duration: 6 months	Patients with treatment-refractory CRS; n=14	Change in SIT-40 score after 6 months, subjective hyposmia symptoms (0 to 3) daily	No	No significant improvement in SIT-40 scores in the treatment group vs controls (p<0.31)
Phosphodiesterase Inhibitors	Hosein & Henkin [551]	2022	Prospective	Intranasal theophylline (20 µg in 0.4 ml saline solution, 1 spray OD, with increasing dosage if no improvement after 2-4 months after to a maximum of 4 sprays / day) (n=39), placebo (saline) (n=39), normal (n=17) Duration: at least 2 months	Patients with normal olfactory function and hyposmia from multiple causes; n=56 12 PIOD 9 PTOD 7 Sinonasal 5 Idiopathic 3 Chemical Exposure 3 Congenital	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)) after at least 2 months of treatment	Yes (DT: all odours, p<0.01, RT: PYR p<0.005, NO2B, THIO, AA p<0.01)	Over half of treated patients experienced a decrease in nasal mucus IL-10 toward control levels after intranasal theophylline administration, correlated with a significant improvement in taste and smell function
Phosphodiesterase Inhibitors	Henkin et al. [554]	2012	Prospective, internally controlled	Oral theophylline anhydrous (200 to 800 mg/day x 2 to 12 months; intranasal theophylline methylpropyl paraben 20 µg/day in each naris x 4 weeks, controls were same group	Patients with olfactory dysfunction of mixed causes; n=10 3 Sinonasal 3 PIOD 2 PTOD 1 Congenital 1 Other	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100)	Yes (DT for Sucrose and Hydrochloride (p<0.01), and Urea, (p<0.05))	Intranasal theophylline treatment improved taste and smell acuity in 8 of 10 patients after 4 weeks, Oral theophylline treatment improved taste and smell acuity in 6 of 10 patients after 2-12 months
Phosphodiesterase Inhibitors	Henkin et al. [550]	2017	Prospective	Oral theophylline (200 to 800 mg taken over 2 to 10 months) (n=44)	Patients with hyposmia from multiple causes; n=44 10 PIOD 15 Sinonasal 9 Congenital 8 PTOD 1 Post-anaesthesia 1 Oropyrosis/Dysgeusia	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective improvement in smell/taste/flavour (0 to 100)	No control group	Significant improvement in subjective responses in smell (p<0.05), taste, and flavour perception and in olfactometry, associated with increased nasal mucus sonic hedgehog and serum theophylline after treatment
Phosphodiesterase Inhibitors	Henkin et al. [553]	2009	Prospective	Oral Theophylline in increasing doses (200, 400, 600, and 800 mg) over 2-8 months	Patients with olfactory dysfunction of mixed causes; n=312 97 PIOD 97 Sinonasal 76 Others 42 PTOD	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100) daily	No control group	Subjective smell loss improved in 157 patients (50.3%), Greater improvement in mean DT and RT before and after treatment (DT: PYR (p<0.001), NO2B (p<0.05), THIO and AA (p<0.01); RT: PYRD and NO2B (p<0.001), NO2B THIO and AA (p<0.01)) at doses of 600 and 800mg of oral theophylline, Improvement persisted as long as treatment was continued (up to 72 months)

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Phosphodiesterase Inhibitors	Meusel et al. [559]	2016	Experimental, placebo- controlled	Espresso with caffeine (65 mg/cup) (n=39); espresso without caffeine (placebo) (n=38)	Patients with sinonasal or PIOD; n=76 48 PIOD 28 Sinonasal	Change in Sniffin' Sticks (TD) score 45 mins after espresso consumption; Subjective smell rating	No	The phosphodiesterase-inhibitor / adenosine-receptor agonist caffeine has little or no short-term effect on olfactory function
Intranasal Calcium Buffers	Whitcroft et al. [685]	2016	Prospective, controlled	Intranasal sodium citrate (1 ml 3.5 g/ 140 ml x 1 dose in the left or right nostril), Placebo (1 ml saline, in the contralateral nostril)	Patients with olfactory dysfunction of mixed causes; n=57 30 Sinonasal 10 Idiopathic 10 PTOD 7 PIOD	Change in monorhinal Sniffin' Sticks (TI) score 20 to 30 minutes after treatment	Yes (PIOD odour identification scores only, p=0.02)	Significantly improved identification scores in patients with post-infectious loss compared to placebo, No significant difference in threshold scores after treatment, Nasal discharge was the most common side effect
Post-traumatic Olfactory Dysfunction								
Corticosteroids	Kim et al. [521]	2017	Retrospective, case series	Oral prednisolone (40 mg x 14 days, tapering by 5 mg daily) (n=60); intranasal mometasone furoate monohydrate spray (2 puffs, 100 µg in each nostril OD) (n=181); Oral prednisolone + intranasal mometasone spray (n=250) Duration: 16 days (Oral prednisolone), 1 month (Intranasal mometasone)	Patients with olfactory dysfunction of mixed causes; n=491 178 PIOD 96 PTOD 94 Sinonasal 89 Idiopathic 23 Previous Sinonasal Surgery 9 Xerostomia 2 Congenital	Change in CCCRCT, CCSIT, subjective rating (recovery vs. no recovery) 1 month after treatment	Yes (p<0.001)	Oral + intranasal and oral corticosteroid groups had better smell recovery outcomes than the intranasal group, No significant difference between oral + intranasal versus oral only (p<0.978)
Corticosteroids	Fleiner et al. [520]	2012	Retrospective	Topical corticosteroid (unspecified drug / dose) + OT (n=18); OT only (n=28) Duration: unspecified	Patients with olfactory dysfunction of mixed causes; n=46 16 PIOD 15 Sinonasal 8 Idiopathic 7 PTOD	Change in Sniffin' Sticks (TDI) scores at 4 or 8 months	Yes (p=0.001 at 8 months)	Statistically clinically significant improvement in TDI scores in the topical corticosteroid + OT group after 8 months of treatment
Corticosteroids	Nguyen & Patel [522]	2018	Prospective, controlled	Intranasal budesonide irrigation (0.5 mg/ 2 ml BID) + OT (n=66); Intranasal saline irrigation (BID) + OT (n=67) Duration: 6 months	Patients with olfactory dysfunction of mixed causes; n=133 62 PIOD 46 Idiopathic 16 PTOD 6 Medication-related 3 Environmental exposure	Clinically significant change in SIT-40 after 6 months	No	Clinically significant change in SIT-40 scores in 35.3% of patients (n=47), Younger age and shorter duration of OD were associated with improvement (p<0.0001)
Corticosteroids	Stenner et al. [509]	2008	Retrospective	Oral beclomethasone (3 to 0.5 mg OD to TID) + topical budesonide (1.5 mg/day, divided into 2 equal doses per side of the nose BID); oral beclomethasone + topical budesonide and neomycin (7.5 mg/day, divided into 2 equal doses per side of the nose BID) Duration: 20 days (Oral beclomethasone), 12 weeks (Topical budesonide only or with Neomycin)	Patients with olfactory dysfunction of mixed causes; n=89 31 PIOD 22 Idiopathic 16 Sinonasal 14 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after 12 weeks	No	No significant difference between TDI scores of treatment and control groups, Improved mean TDI scores with oral steroids across all treatment groups, with benefit from topical corticosteroids +/ antibiotic influenced by initial oral steroid responsiveness
Corticosteroids	Bratt et al [507]	2020	Prospective	Oral prednisolone (30 mg OD), then OT only Duration: 10 days (Oral prednisolone); 3 months (OT)	Patients with PTOD; n=22	Change in Sniffin' Sticks (TDI) score after 10 days, 3, and 12 months	No control group	Clinically significant (≥6) improvement in composite threshold, discrimination, and identification score in 50% of participants after 1 year (p<0.001)
Corticosteroids	Jiang et al. [690]	2010	Prospective	Oral prednisolone (15 mg QID x 3 days, then 10 mg QID x 3 days, 10 mg TID x 3 days, tapering by 10 mg/day every 3 days) Duration: 15 days	Patients with PTOD; n=116	Change in PEA threshold test (monthly for 3 months after treatment)	No control group	Improvement in only 16.4% of patients; spontaneous recovery cannot be ruled out, Patients whose thresholds improved were significantly younger (p=0.033)

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Corticosteroids	Heilmann et al. [513]	2004	Prospective	Oral prednisolone (40 mg/day, tapering doses over 21 days) (n=85); intranasal mometasone (2 sprays OD in each nostril) (n=76); oral Vitamin B complex (thiamine 12 mg, riboflavin 12 mg, pyridoxine 0.75 mg, nicotinamide 60 mg, calcium pantothenate 6 mg 2 capsules TID) (n=31) Duration: 21 days (Oral prednisolone), 6 months (Intranasal mometasone and Vitamin B complex)	Patients with olfactory dysfunction of mixed causes; n=192 85 Idiopathic 72 PIOD 19 Sinonasal 10 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after an average of 2 and 6 months	No control group	Improvement following oral and intranasal corticosteroids (p<0.001, p=0.03 respectively); improvement with oral Vitamin B only after 6 months (p=0.001) but not after 2 months (p=0.07)
Corticosteroids	Fujii et al. [505]	2002	Prospective	Dexamethasone septal injection (4 mg/0.5 ml every 2 weeks x 8 times)	Patients with PTOD; n=27	Change in T&T olfactometer threshold, Alinamin test score after 4 months	No control group	Improvement of detection thresholds in 6 patients, improvement of recognition thresholds in 4 patients
Phosphodiesterase Inhibitors	Hosein & Henkin [551]	2022	Prospective	Intranasal theophylline (20 µg in 0.4 ml saline solution, 1 spray OD, with increasing dosage if no improvement after 2-4 months after to a maximum of 4 sprays / day) (n=39), placebo (saline) (n=39), normal (n=17) Duration: at least 2 months	Patients with normal olfactory function and hyposmia from multiple causes; n=56 12 PIOD 9 PTOD 7 Sinonasal 5 Idiopathic 3 Chemical Exposure 3 Congenital	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)) after at least 2 months of treatment	Yes (DT: all odours, p<0.01, RT: PYR p<0.005, NO2B, THIO, AA p<0.01)	Over half of treated patients experienced a decrease in nasal mucus IL-10 toward control levels after intranasal theophylline administration, correlated with a significant improvement in taste and smell function
Phosphodiesterase Inhibitors	Henkin et al. [554]	2012	Prospective, internally controlled	Oral theophylline anhydrous (200 to 800 mg/day x 2 to 12 months; intranasal theophylline methylpropyl paraben 20 µg/day in each naris x 4 weeks, controls were same group	Patients with olfactory dysfunction of mixed causes; n=10 3 Sinonasal 3 PIOD 2 PTOD 1 Congenital 1 Other	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100)	Yes (DT for Sucrose and Hydrochloride (p<0.01), and Urea, (p<0.05))	Intranasal theophylline treatment improved taste and smell acuity in 8 of 10 patients after 4 weeks, Oral theophylline treatment improved taste and smell acuity in 6 of 10 patients after 2-12 months
Phosphodiesterase Inhibitors	Henkin et al. [550]	2017	Prospective	Oral theophylline (200 to 800 mg taken over 2 to 10 months) (n=44)	Patients with hyposmia from multiple causes; n=44 10 PIOD 15 Sinonasal 9 Congenital 8 PTOD 1 Post-anaesthesia 1 Oropyrosis/Dysgeusia	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective improvement in smell/taste/flavour (0 to 100)	No control group	Significant improvement in subjective responses in smell (p<0.05), taste, and flavour perception and in olfactometry, associated with increased nasal mucus sonic hedgehog and serum theophylline after treatment
Phosphodiesterase Inhibitors	Henkin et al. [553]	2009	Prospective	Oral Theophylline in increasing doses (200, 400, 600, and 800 mg) over 2-8 months	Patients with olfactory dysfunction of mixed causes; n=312 97 PIOD 97 Sinonasal 76 Others 42 PTOD	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)), Subjective Smell Rating (0 to 100) daily	No control group	Subjective smell loss improved in 157 patients (50.3%), Greater improvement in mean DT and RT before and after treatment (DT: PYR (p<0.001), NO2B (p<0.05), THIO and AA (p<0.01); RT: PYRD and NO2B (p<0.001), NO2B THIO and AA (p<0.01)) at doses of 600 and 800mg of oral theophylline, Improvement persisted as long as treatment was continued (up to 72 months)
Intranasal Calcium Buffers	Philpott et al. [566]	2017	Prospective, controlled	Sodium citrate solution (0.5 ml in each nostril x 1 dose) (n=31); Placebo (sterile water, 0.5 ml in each nostril x 1 dose) (n=24)	Patients with olfactory dysfunction of mixed causes; n=55 21 PIOD 13 Idiopathic 4 PTOD	Change in phenyl ethyl alcohol, 1-butanol, eucalyptol, and acetic acid thresholds every 15 minutes up to a maximum of 2 hours	Yes (all odours except acetic acid, p<0.05)	Improved threshold scores in the treatment group compared to controls for 3 out of 4 odours tested, but effect is transient, peaking at 30-60 minutes after application, Rhinorrhoea and Sore throat were frequently reported side effects

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Intranasal Calcium Buffers	Panagiotopoulos et al. [564]	2005	Prospective	Sodium citrate buffer solution (3.5 g/140 ml x 1 dose) to the nasal cleft using head down and forwards position, Epinephrine (1 mg/ml, 1ml in each nostril x 1 dose), placebo (saline, 1ml in each nostril x 1 dose)	Patients with olfactory dysfunction of mixed causes; n=31 18 PIOD 7 Post-nasal surgery 1 PTOD 5 Unspecified	Change in Sniffin' Sticks 12-item screening test Day 1 olfaction evaluated 2 times (no medication and saline) Days 2 and 3 olfaction evaluated before and every 15 minutes after 1cc in each nostril of epinephrine (day 2) and sodium citrate buffer (day 3), for 1 hour	No	Significantly higher scores compared to baseline after administration of buffer solution (p<0.0001), Measured improvement in 97% of patients within one hour; 74% noticed improvement, with a median duration of 3 hours, Itching was the most common side effect
Intranasal Calcium Buffers	Whitcroft et al. [685]	2016	Prospective, controlled	Intranasal sodium citrate (1 ml 3.5 g/ 140 ml x 1 dose in the left or right nostril), Placebo (1 ml saline, in the contralateral nostril)	Patients with olfactory dysfunction of mixed causes; n=57 30 Sinonasal 10 Idiopathic 10 PTOD 7 PIOD	Change in monorhinal Sniffin' Sticks (TI) score 20 to 30 minutes after treatment	Yes (PIOD odour identification scores only, p=0.02)	Significantly improved identification scores in patients with post-infectious loss compared to placebo, No significant difference in threshold scores after treatment, Nasal discharge was the most common side effect
Zinc	Jiang et al. [511]	2015	Prospective, controlled	Zinc gluconate (10 mg TID x 1 month) + prednisolone (1 mg/kg/day then tapering for 2 weeks) (n=39); zinc only (10 mg TID x 1 month) (n=35); prednisolone only (n=34); no treatment (n=37)	Patients with post-traumatic anosmia; n=145	Change in Phenyl ethyl alcohol odour detection threshold test monthly up to a mean of 5 to 6 months after, MRI for OB measurement 2 months after treatment	Yes (recovery rates: p=0.006 for zinc + prednisolone, p=0.013 for zinc only)	Zinc + steroid application and zinc only groups showed significant threshold improvement compared to "no treatment"
Novel Treatments	Hummel et al. [686]	2017	Retrospective cohort	Topical vitamin A (10,000 IU OD) + OT (n=124), OT only (n=46) Duration: 8 weeks	Patients with PIOD and PTOD; n=170 102 PIOD 68 PTOD	Change in Sniffin' Sticks (TDI) score after approximately 10 months	Yes (Odour discrimination higher for Vitamin A + OT for all patients, p=0.008; PIOD odour threshold and discrimination scores higher for Vitamin A + OT, p=0.01 and p=0.04 respectively	Vitamin A + OT group had significantly higher odour discrimination scores for all patients; and significantly higher threshold and discrimination scores in the post-infectious group
Novel Treatments	Reden et al. [631]	2012	Prospective, controlled	Oral vitamin A (10,000 IU OD x 3 months) (n=26) or placebo (n=26)	Patients with PIOD and PTOD; n=52 33 PIOD 19 PTOD	Change in Sniffin' Sticks (TDI) score after mean of 5 months	No	No significant difference between treatment and controls
Novel Treatments	Quint et al. [689]	2002	Prospective, controlled	Caroverine (120 mg/day) (n=51), Control: zinc sulfate (400 mg/day) (n=26) Duration: 4 weeks	Patients with olfactory dysfunction of mixed causes; n=77 38 PIOD 25 Idiopathic 14 PTOD	Change in Sniffin Sticks' (TDI) score, after 4 weeks	Unspecified	Significant improvement of odour thresholds among anosmics (p=0.005) and odour identification for all patients (Anosmia: p=0.038, Hyposmia: p=0.041), Zinc did not result in any significant measurable improvement in olfaction
Idiopathic Olfactory Dysfunction								
Corticosteroids	Kim et al. [521]	2017	Retrospective, case series	Oral prednisolone (40 mg x 14 days, tapering by 5 mg daily) (n=60); intranasal mometasone furoate monohydrate spray (2 puffs, 100 µg in each nostril OD) (n=181); Oral prednisolone + intranasal mometasone spray (n=250) Duration: 16 days (Oral prednisolone), 1 month (Intranasal mometasone)	Patients with olfactory dysfunction of mixed causes; n=491 178 PIOD 96 PTOD 94 Sinonasal 89 Idiopathic 23 Previous Sinonasal Surgery 9 Xerostomia 2 Congenital	Change in CCCRCT, CCSIT, subjective rating (recovery vs. no recovery) 1 month after treatment	Yes (p<0.001)	Oral + intranasal and oral corticosteroid groups had better smell recovery outcomes than the intranasal group, No significant difference between oral + intranasal versus oral only (p<0.978)

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Corticosteroids	Fleiner et al. [520]	2012	Retrospective	Topical corticosteroid (unspecified drug / dose) + OT (n=18); OT only (n=28) Duration: unspecified	Patients with olfactory dysfunction of mixed causes; n=46 16 PIOD 15 Sinonasal 8 Idiopathic 7 PTOD	Change in Sniffin' Sticks (TDI) scores at 4 or 8 months	Yes (p=0.001 at 8 months)	Statistically clinically significant improvement in TDI scores in the topical corticosteroid + OT group after 8 months of treatment
Corticosteroids	Heilmann et al. [519]	2004	Retrospective	Intranasal mometasone spray (2 sprays OD, ~0.1 mg per nostril) x 1 to 3 months) (n=37); oral prednisolone (40 mg/ day, tapering doses over 21 days) (n=55) Duration: 1 to 3 months (Intranasal mometasone), 21 days (Oral prednisolone)	Patients with olfactory dysfunction of mixed causes; n=92 58 Idiopathic 22 PIOD 12 Sinonasal	Change in Sniffin' Sticks (TDI) scores after 21 to 330 days	Yes (p<0.001)	Treatment with oral prednisolone led to significantly improved TDI scores regardless of aetiology (p<0.001), intranasal mometasone had no significant effect on olfaction
Corticosteroids	Nguyen & Patel [522]	2018	Prospective, controlled	Intranasal budesonide irrigation (0.5 mg/ 2 ml BID) + OT (n=66); Intranasal saline irrigation (BID) + OT (n=67) Duration: 6 months	Patients with olfactory dysfunction of mixed causes; n=133 62 PIOD 46 Idiopathic 16 PTOD 6 Medication-related 3 Environmental exposure	Clinically significant change in SIT-40 after 6 months	No	Clinically significant change in SIT-40 scores in 35.3% of patients (n=47), Younger age and shorter duration of OD were associated with improvement (p<0.0001)
Corticosteroids	Stenner et al. [509]	2008	Retrospective	Oral beclomethasone (3 to 0.5 mg OD to TID) + topical budesonide (1.5 mg/day, divided into 2 equal doses per side of the nose BID); oral beclomethasone + topical budesonide and neomycin (7.5 mg/day, divided into 2 equal doses per side of the nose BID) Duration: 20 days (Oral beclomethasone), 12 weeks (Topical budesonide only or with Neomycin)	Patients with olfactory dysfunction of mixed causes; n=89 31 PIOD 22 Idiopathic 16 Sinonasal 14 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after 12 weeks	No	No significant difference between TDI scores of treatment and control groups, Improved mean TDI scores with oral steroids across all treatment groups, with benefit from topical corticosteroids +/ antibiotic influenced by initial oral steroid responsiveness
Corticosteroids	Blomqvist et al. [518]	2003	Prospective, controlled	Oral prednisolone (40 mg/day x 3 days, tapering by 5 mg daily), then either Intranasal fluticasone spray (2 sprays, 100 µg OD in each nostril) (n=20); placebo spray (water, avisel, polysorbate 80, glucose, benzalkonium chloride (198 µg/g) and phenyl ethyl alcohol (2.5 mg/g) (n=10); no treatment (n=10) Duration: 10 days (Oral prednisolone), 6 months (Intranasal fluticasone, placebo)	Patients with olfactory dysfunction of mixed causes; n=40 23 PIOD 10 Sinonasal 7 Unknown/Idiopathic	Change in CC-CRCT, VAS after 10 days, 2, 6 months)	No	Significant improvement after the initial treatment with oral corticosteroids, no significant difference in olfactory threshold scores between treatment and control groups after 10 days, 2 and 6 months
Corticosteroids	Schriever et al. [510]	2012	Retrospective	Oral methyl-prednisolone (40 mg, then tapering by 5 mg every other day) Duration: 15 days	Patients with olfactory dysfunction of mixed causes; n=425 221 Sinonasal 157 Idiopathic 27 PIOD 20 PTOD, Post-surgical, Others)	Change in Sniffin' Sticks (TDI) scores after 15 days	No control group	Greater and clinically significant increase in TDI scores among patients with nasal polyps (p<0.001) who received treatment, PIOD (p=0.003) and idiopathic (p=0.01) patients who received corticosteroids also significantly improved but the improvement was less than those with sinonasal causes

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Corticosteroids	Heilmann et al. [513]	2004	Prospective	Oral prednisolone (40 mg/day, tapering doses over 21 days) (n=85); intranasal mometasone (2 sprays OD in each nostril) (n=76); oral Vitamin B complex (thiamine 12 mg, riboflavin 12 mg, pyridoxine 0.75 mg, nicotinamide 60 mg, calcium pantothenate 6 mg 2 capsules TID) (n=31) Duration: 21 days (Oral prednisolone), 6 months (Intranasal mometasone and Vitamin B complex)	Patients with olfactory dysfunction of mixed causes; n=192 85 Idiopathic 72 PIOD 19 Sinonasal 10 PTOD 6 Others	Change in Sniffin' Sticks (TDI) scores after an average of 2 and 6 months	No control group	Improvement following oral and intranasal corticosteroids (p<0.001, p=0.03 respectively); improvement with oral Vitamin B only after 6 months (p=0.001) but not after 2 months (p=0.07)
Phosphodiesterase Inhibitors	Hosein & Henkin [551]	2022	Prospective	Intranasal theophylline (20 µg in 0.4 ml saline solution, 1 spray OD, with increasing dosage if no improvement after 2-4 months after to a maximum of 4 sprays / day) (n=39), placebo (saline) (n=39), normal (n=17) Duration: at least 2 months	Patients with normal olfactory function and hyposmia from multiple causes; n=56 12 PIOD 9 PTOD 7 Sinonasal 5 Idiopathic 3 Chemical Exposure 3 Congenital	Change in Olfactometry of 4 odours: (Detection (DT) and Recognition (RT) thresholds, magnitude estimation (ME) and hedonic evaluation (H)) after at least 2 months of treatment	Yes (DT: all odours, p<0.01, RT: PYR p<0.005, NO2B, THIO, AA p<0.01)	Over half of treated patients experienced a decrease in nasal mucus IL-10 toward control levels after intranasal theophylline administration, correlated with a significant improvement in taste and smell function
Intranasal Calcium Buffers	Philpott et al. [566]	2017	Prospective, controlled	Sodium citrate solution (0.5 ml in each nostril x 1 dose) (n=31); Placebo (sterile water, 0.5 ml in each nostril x 1 dose) (n=24)	Patients with olfactory dysfunction of mixed causes; n=55 21 PIOD 13 Idiopathic 4 PTOD	Change in phenyl ethyl alcohol, 1-butanol, eucalyptol, and acetic acid thresholds every 15 minutes up to a maximum of 2 hours	Yes (all odours except acetic acid, p<0.05)	Improved threshold scores in the treatment group compared to controls for 3 out of 4 odours tested, but effect is transient, peaking at 30-60 minutes after application, Rhinorrhoea and Sore throat were frequently reported side effects
Intranasal Calcium Buffers	Whitcroft et al. [685]	2016	Prospective, controlled	Intranasal sodium citrate (1 ml 3.5 g/ 140 ml x 1 dose in the left or right nostril), Placebo (1 ml saline, in the contralateral nostril)	Patients with olfactory dysfunction of mixed causes; n=57 30 Sinonasal 10 Idiopathic 10 PTOD 7 PIOD	Change in monorhinal Sniffin' Sticks (TI) score 20 to 30 minutes after treatment	Yes (PIOD odour identification scores only, p=0.02)	Significantly improved identification scores in patients with post-infectious loss compared to placebo, No significant difference in threshold scores after treatment, Nasal discharge was the most common side effect
Other Causes of Olfactory Dysfunction								
Novel Treatments	Yan et al. [656]	2020	Prospective, controlled	Intranasal saline irrigation (BID) + omega 3 (1000 mg/ capsule, 1 capsule BID) (n=46); intranasal saline irrigation only (n=41)	Patients who underwent endoscopic sellar or parasellar tumour resection; n=87	Change in SIT-40 score at 6 weeks, 3, and 6 months	Yes (3 months, p=0.02; 6 months, p=0.01)	Patients taking omega-3 were less likely to have post-operative olfactory loss compared to controls
Phosphodiesterase Inhibitors	Gudziol & Hummel [691]	2009	Prospective	Intravenous pentoxifylline (200 mg, dissolved in 500 ml of 0.9% sodium solution, BID infused for 2 hours (n=15)); oral pentoxifylline (200 mg TID) (n=4)	Patients being treated for inner ear conditions; n=19	Sniffin' Sticks (TDI) score; Subjective smell rating (very good, good, normal, poor, very poor, or complete loss) 1 to 2 hours after administration of pentoxifylline	Yes (p=0.01, Odour threshold)	Improvement in odour thresholds after administration of pentoxifylline, with greater improvement in younger patients (p=0.001)
Zinc	Lyckholm et al. [692]	2012	Prospective, controlled	Oral zinc (220 mg BID, ~50 mg elemental zinc BID) (n=20); placebo (lactose monohydrate BID) (n=21)	Chemotherapy-related smell disorders; n=41	Change in Subjective smell rating (0 to 100) at 1, 2, and 3 months after starting treatment	No	There was non-significant worsening of smell loss over time
Monoamine Oxidase B Inhibitors	Haehner et al. [693]	2015	Cross-sectional, controlled	Rasagiline therapy for at least 4 months (n=74), Non-rasagiline therapy (n=150)	Patients with Parkinson's disease; n=224	Change in Sniffin' Sticks (TDI) scores	Yes (only for PD <5 years, odour discrimination, p=0.04)	Rasagiline treated patients presented with significantly better odour discrimination when Parkinson's disease duration was less than 8 years

Drug Class	Author	Year	Study Type	Treatment Method	Study Population; n	Outcome Measures	Statistically Significant Between Treatment Groups (Y/N)	Results
Monoamine Oxidase B Inhibitors	Haehner et al. [694]	2013	Prospective, controlled	Rasagiline (1 mg OD) (n=17), placebo (n=17) Duration: 120 days	Patients with Parkinson's disease; n=34	Change in Sniffin' Sticks (TDI) score, retronasal flavour powders test, OERP, after 120 days of treatment	No	No significant difference in TDI scores between the treatment and control groups, but with a significant increase in TDI score between baseline and after 120 days for the rasagiline group (p=0.004)
Novel Treatments	Rondanelli et al. [655]	2012	Prospective, controlled	Dietary supplement (DHA 720 mg, EPA 286 mg, Vitamin E 16 mg, Soy phospholipids 160 mg, Tryptophan 95 mg, and melatonin 5 mg, 2 capsules OD, 1 hour before bedtime) (n=11); placebo (n=14) Duration: 12 weeks	Patients with mild cognitive impairment; n=25	Change in Sniffin' Sticks 12-item screening test after 12 weeks	Yes (Odour identification, p<0.0096)	Significantly higher identification scores for supplementation group
Phosphodiesterase Inhibitors	Gudziol et al. [558]	2007	Crossover study	Sildenafil (50 mg) on day 0, then Sildenafil 100 mg) at day 4 and 8; placebo (starch) at day 4 and 8 Duration: 8 days	Healthy participants; n=20	Change in Sniffin' Sticks (TDI) scores on day 4 and 8	Yes (p=0.007, for 100 mg Sildenafil)	Higher sildenafil doses produced decreased olfactory scores compared to placebo

colleagues investigated the utility of systemic prednisolone in treating 9 patients with topical corticosteroid-resistant PIOD [500]. The authors demonstrated no significant improvement in T&T olfactometer detection or recognition thresholds. In 2005, Fukazawa described results of septal corticosteroid injection (dexamethasone or betamethasone) in a case series of 133 patients with PIOD [501]. 49.6% of patients achieved clinical improvement – defined as an average improvement in T&T olfactometer recognition threshold of 1 point. However, this study did not include a control group. Given the known possibility of spontaneous recovery in PIOD, this limits its interpretation. Specifically with regards to C19OD, Le Bon and colleagues compared OT (n=18) to OT + methylprednisolone (n=9, 32mg once daily for 10 days) using the "Sniffin' Sticks" composite TDI score in a prospective non-randomised trial [502]. After 10 weeks of training, there was a significantly greater increase in TDI score within the OT + corticosteroid group than the OT group. Furthermore, within the OT + corticosteroid group, the mean TDI improved by 7.7 points, therefore reaching both statistical and clinical significance. Vaira and colleagues performed a small multi-site randomised case-control study assessing the efficacy of oral prednisolone (15 day tapering dose) + intranasal irrigation with betamethasone, ambroxol (a mucolytic) and rinazine (a decongestant) (all for 15 days) compared with no treatment (n=9 in each group) [503]. They demonstrated significantly higher CCCRCT scores at both interim (20 day) and final (40 day) assessment periods in the treatment group, compared to control. However, it is difficult to disentangle the potential treatment effects of the different medications used in the intervention arm of this study, which is also limited by a small sample size. Recent work from Genetzaki and colleagues showed improved psychophysical test scores in 19% of PIOD patients treated with a two-week course of oral methylprednisolone + OT vs OT alone [504]. Post-hoc testing demonstrated evidence of inflammation in half of those who had improved – either residual from the infectious event or as evidence of parallel CRS (the latter being supported by the high prevalence of this condition in the general population). This highlights the importance of excluding underlying inflammation in PIOD, and associated potential benefit of systemic corticosteroids for those in whom such evidence exists.

Several studies have also specifically addressed the use of systemic corticosteroids in PTOD. In 2002, Fujii et al., injected dexamethasone 8 times (with 2 weekly intervals) into the septal mucosa of 27 patients with PTOD (61.5% anosmic, 38.4% hyposmic) [505]. Using the T&T olfactometer, they demonstrated improvement in detection threshold in 6 and recognition threshold in 4 out of 18 patients who followed up – patients treated within 2 months of initial head injury were found to have better outcomes. Later, in 2010, Jiang et al. assessed threshold scores following administration of high dose systemic prednisolone, in 116 patients with PTOD [506]. Improved PEA threshold scores were demonstrated in 16.4% of the study population (mean follow up period 5.5 months), with better outcomes in younger patients. Again in patients with PTOD, Bratt and colleagues demonstrated a clinically significant improvement in "Sniffin' Sticks" TDI score in 50% of participants (total n=22) at 1 year following treatment with 10 days of systemic prednisolone (30mg once daily), followed by 3 months of OT [507]. However, none of these studies included a control group. Though the spontaneous recovery rate in PTOD is less than in PIOD, this still limits interpretation of the results. Jiang and colleagues reported results from a further study in 2015: a randomised controlled trial investigating the effect of oral prednisolone and zinc, alone or in combination, compared with no-treatment control, on odour thresholds in patients with PTOD [508]. There was no statistically

significant difference in odour threshold between corticosteroid and control group. However, treatment with prednisolone + zinc or zinc alone was superior to control.

The use of systemic corticosteroids in mixed patient cohorts has also been addressed. Where patients with sinonasal disease-related OD are included and subgroup analysis by aetiology is not performed, this makes interpretation of these studies difficult. In 2008, Stenner and colleagues investigated the utility of oral beclomethasone followed by topical budesonide or topical budesonide + neomycin in the treatment of OD of mixed causes [509]. The demonstrated improved composite TDI score (from 15.5 to 18.7) after treatment with oral corticosteroids, was observed among all patients (including those with sinonasal disease-related OD). However, the authors did comment that 'steroid-responsiveness (SR)' was dependent on the underlying aetiology – with sinonasal disease representing the greatest proportion of SR patients, and PTOD the least. The distribution of steroid-responsiveness and non-steroid-responsiveness was approximately equal for PIOD and idiopathic loss. Furthermore, there appeared to be no additional benefit in the use of topical corticosteroids. In 2012, Schriever et al. published results from a retrospective analysis of psychophysical olfactory scores before and after treatment with 14 days of systemic methylprednisolone. Patients with OD of any cause were included, though the majority (52%) had olfactory loss secondary to sinonasal disease. Overall, 26.6% of patients improved by more than 6 points on TDI testing (the MCID) [510]. Interpretation of these studies is limited, both by inclusion of multiple aetiologies and lack of appropriate control groups.

Systemic corticosteroids have also been combined with other agents, namely Zinc (as described above), vitamin B, and Ginkgo biloba [511–513]. These studies suggest a possible additive benefit for the former two, though the additional benefit from Ginkgo biloba did not reach statistical significance.

When considering use of systemic corticosteroids, the risk of side effects must be taken into account [514–516]. These include: **gastrointestinal** – gastritis, ulcer formation, bleeding; **musculoskeletal** – osteoporosis, steroid-induced myopathy, osteonecrosis; **metabolic/endocrine** - increased blood glucose levels and impaired glycaemic control in diabetics, weight gain/development of Cushingoid features/Cushing syndrome, HPA axis suppression; **immune system** – immunosuppression; **cardiovascular** – premature atherosclerosis; **ophthalmological** – cataracts, glaucoma; **neuropsychiatric** – mood (hypomania, anxiety, depression) and sleep disturbance, rarely psychosis. At present, evidence-based guidelines regarding the acceptable frequency of systemic corticosteroid use do not exist. It, therefore, falls to the individual clinician to exercise the appropriate prudence, particularly in cases of non-CRS-related olfactory loss, where the evidence supporting corticosteroid use is poor [517].

Intranasal corticosteroids

The use of intranasal corticosteroid therapy has been trialled with varying results, alone and in combination with other therapeutic approaches. The following studies assessed use of intranasal corticosteroids in mixed aetiology patient cohorts.

An early double-blind, randomised controlled trial by Blomqvist and colleagues demonstrated no significant difference in odour threshold score following 6 months of treatment with intranasal fluticasone spray, placebo spray, or no treatment (n=20, n=10, n=10 respectively), in patients with OD of mixed causes [518]. Of note, all patients in this trial had undergone initial preloading with systemic prednisolone + intranasal fluticasone for 10 days. In 2004, Heilmann and colleagues performed a retrospective review of patients with sinonasal disease-related OD, PIOD or idiopathic OD treated with either topical mometasone spray (1-3 months) or oral prednisolone (21 day tapering dose) [519]. Across all patients, and within the PIOD and idiopathic subgroups, there was no significant improvement in "Sniffin' Sticks" composite TDI score after treatment with topical mometasone. Treatment with oral prednisolone, however, led to significantly improved TDI scores, irrespective of aetiology. Treatment outcomes in this study were not affected by presence of parosmia at baseline. In 2012, Fleiner and colleagues performed a retrospective analysis of patients with OD of mixed causes, who were treated with either olfactory training (OT) alone or OT + topical corticosteroid. They demonstrated a statistically and clinically significant improvement in "Sniffin' Sticks" composite TDI scores in the OT + corticosteroid group (n=18), but not within the OT only group (n=28) [520]. These changes were driven by the PIOD subgroup – no significant improvements from baseline were seen in patients with sinonasal, post-traumatic or idiopathic OD. In 2017, Kim and colleagues retrospectively demonstrated improved outcomes in patients with OD of mixed causes (n=491) who were treated with systemic corticosteroids ± topical corticosteroids compared with topical corticosteroids alone (outcomes assessed using CCCRCT and CC-SIT) [521]. There was no significant difference in outcomes when comparing systemic corticosteroid vs. systemic + topical corticosteroid groups. No subgroup analysis comparing treatment outcomes within individual aetiology subgroups was performed, though overall, PIOD patients showed the greatest level of improvement. In studies without subgroup analysis by aetiology, as described for systemic corticosteroid use above, it is difficult to interpret findings as results may be driven by sinonasal disease-related OD.

In a study excluding sinonasal disease, Nguyen and Patel performed a randomised controlled trial comparing OT + intranasal budesonide irrigation with OT + intranasal saline irrigation, in

133 patients (OT + budesonide n=66, OT + saline n=67) with OD of mixed causes (PIOD, PTOD, idiopathic, medication-related, environmental) [522]. After 6 months, significantly more patients in the OT + budesonide group achieved a clinically significant improvement in odour identification scores (SIT-40) than in the OT + saline group (OT + budesonide proportion improved = 43.9%, OT + saline = 26.9%, p=0.039). Subgroup analysis according to aetiology was not performed. Additionally, participants in this study were described as 'anosmic' but no information was provided regarding baseline SIT-40 scores in either treatment or control group.

Specifically with regards to C19OD, Kasiri and colleagues performed a double-blind, randomised controlled trial comparing intranasal mometasone furoate spray + OT (n=39) with intranasal sodium chloride + OT (n=38) in non-hospitalised patients [523]. After 4 weeks of treatment, there was no statistically significant difference in mean change in odour identification score (Iran Smell Identification Test) between groups. However, there were more patients with severe OD within the control vs treatment group at the study end point. It should be noted, however, that 4 weeks is a short duration for OT. Abdelalim and colleagues performed a larger randomised controlled trial in 100 patients with C19OD, 50 of whom were treated with OT and 50 of whom were treated with OT + intranasal mometasone spray [524]. The authors demonstrated no significant difference in olfactory outcomes (VAS) in the treatment group, compared to the control group. However, this study is limited by lack of psychophysical olfactory testing, as well as short OT/follow up times (3 weeks). In their single-centre RCT, Yildiz and colleagues demonstrated improved subjective olfactory outcomes ('Subjective Olfactory Capability (SOC)' - a patient reported outcome measure) following 30 days treatment with intranasal triamcinolone + saline (n=50) versus saline alone (n=50) or no intranasal treatment (n=50) in patient with C19OD [525]. In another single centre RCT, Tragoonrungsea and colleagues demonstrated no significant difference in subjective olfaction following treatment with OT alone (n=71), OT + saline irrigation (n=70) or OT + budesonide irrigation (n=72) [526]. When interpreting the results of such studies, it is important to note the duration of disease prior to participant recruitment. This is particularly important in the case of C19OD, in which a large proportion of patients will go on to fully recover, and in which different mechanisms may be implicated at early/late stages. With regards to the above-described studies, it is important to note that the duration of existing C19OD, and treatment periods, were sufficiently short to preclude generalisation to post-C19OD/PIOD.

Finally, it has been shown that application technique affects the distribution of medications within the nasal cavity [479,527]. With this in mind, Nguyen and Patel performed a randomised controlled trial comparing OT + intranasal budesonide irrigation with OT + intranasal saline irrigation, in 133 patients (OT + budesonide n=66, OT + saline n=67) with OD of mixed causes (PIOD, PTOD, idiopathic, medication-related, environmental) [522]. After 6 months, significantly more patients in the OT + budesonide group achieved a clinically significant improvement in odour identification scores (SIT-40) than in the OT + saline group (OT + budesonide proportion improved = 43.9%, OT + saline = 26.9%, p=0.039). Subgroup analysis according to aetiology was not performed. Additionally, participants in this study were described as 'anosmic' but no information was provided regarding baseline SIT-40 scores in either treatment or control group. These results should be compared to those from Tragoonrungsea et al., who did not demonstrate significant treatment effect with budesonide irrigation in C19OD (see above [526]).

Overall, evidence regarding corticosteroid use for non-sinonasal OD is poor (see also [528]) – in part due to lack of well-designed, rigorous studies focussing on aetiology-specific OD. Despite this, systemic ± topical corticosteroids are frequently used for the treatment of non-sinonasal OD: in 2004 89% of European clinicians favoured topical corticosteroids irrespective of aetiology [210] and in 2020 systemic and topical corticosteroids were amongst the most popular treatments for PIOD amongst members of the Clinical Olfactory Working Group (COWoG) [477]. This practice is also reflected in patient-reported treatment regimens for PIOD [529]. Further work is required to justify this continued practice.

Recommendations:

➢ Systemic (short courses) and/or intranasal (long-term) corticosteroids should be prescribed in patients with olfactory dysfunction secondary to CRS, severe allergic rhinitis, and other inflammatory conditions according to existing clinical guidelines.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)

➢ There is limited evidence to support use of systemic or intranasal corticosteroids for other causes of olfactory dysfunction, but if topical corticosteroids are used, a delivery mechanism that can reach the olfactory cleft (i.e., rinses in place of sprays) would be recommended.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.5)

➢ Potential side effects and contraindications should be taken into account when prescribing systemic corticosteroids.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.9)

Monoclonal Antibodies (Biologics)

Monoclonal antibodies (biologics) are a class of medication increasingly used in the modulation of CRS-related type II inflammation. The use of biologics within this setting is extensively covered by the updated Position Paper on Rhinosinusitis and Nasal Polyps [85] and a recent Cochrane review [530]. We therefore

present a limited discussion of olfactory outcomes in relation to these drugs.

Dupilumab is a human monoclonal antibody to the Interleukin (IL)-4 alpha subunit, which inhibits IL-4 and IL-13 signalling, and is approved for use in CRSwNP. Bachert and colleagues reported results from LIBERTY NP SINUS-24 and LIBERTY-NP SINUS-52 in 2019: two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 dupilumab trials in patients with severe CRSwNP [531]. They demonstrated endpoints of significantly improved odour identification scores (SIT-40) and patient-reported loss of smell in the treatment groups compared with controls. These olfactory outcomes were explored in more detail by Mullol and colleagues in 2022, who performed a pooled analysis of the 724 patients across the two trials [532]. They demonstrated rapid (subjective scores improved by day 3) and sustained improvement in olfactory function (mean SIT-40 score improvement 10.5 at 24 weeks) in the dupilumab group, compared to control. These results were independent of various potential confounding factors, such as disease duration, previous surgery and co-morbid respiratory disease status Similar results have also been demonstrated in early 'real-life' studies of dupilumab in patients with CRSwNP (including surgically naïve) [533–536].

Omalizumab is a recombinant humanised monoclonal antibody that binds to free circulating IgE, so reducing expression of IgE receptors on mast cells, dendritic cells and basophils, and thereby inhibiting their activation. In 2010, Pinto and colleagues performed a double-blind, placebo-controlled, randomised trial in 14 patients with treatment refractory CRS (treatment n=7, control n=7) [537]. After 6 months of treatment with omalizumab, there was no significant improvement in SIT-40 scores, compared with controls. In 2013, Gevaert et al., also conducted a small double-blind, placebo-controlled, randomised trial (24 patients with CRSwNP, treatment n=16, control n=8) [538]. They demonstrated significantly improved subjective symptoms scores for 'loss of smell' in the treatment group but did not test olfactory function using psychophysical tools. Results from the replicate omalizumab phase 3 trials in corticosteroid-refractive CRSwNP, POLYP1 (n=138, 72-treatment arm, 66-placebo arm) and POLYP2 (n=127 , 62-treatment arm, 72-placebo arm), are now available [539,540]. At 24 weeks, there were statistically significant improvements in SIT-40 and patient reported 'loss of smell' scores (POLYP 1 - SIT-40 treatment arm difference 3.81 (95% CI = 1.38-6.24), p=0.0024, loss of smell score treatment arm difference –0.33 (95% CI = –0.60 to –0.06), p=0.02; POLYP 2 - SIT-40 treatment arm difference 3.86 (95% CI = 1.57-6.15), p=0.001, loss of smell score treatment arm difference –0.45 (95% CI = –0.73 to –0.16)), p=0.002) [539]. At 52 weeks, omalizumab use (either continued treatment or switch from placebo to treatment arm) was associated with further improvements in psychophysical and patient reported olfactory function, which then deteriorated following treatment cessation [540].

Mepolizumab is an anti-IL5 monoclonal antibody that interferes with eosinophil differentiation and survival. In a double-blind, placebo-controlled, randomised trial, Bachert and colleagues demonstrated significantly improved subjective olfactory scores after 25 weeks of treatment with mepolizumab (in addition to intranasal corticosteroids) in patients with CRSwNP (treatment n=42, control n=32) [541]. However, there was no significant improvement in odour identification scores (12-item screening Sniffin Sticks) with treatment. In a double-blind, placebo-controlled, randomised trial in 30 patients with corticosteroid-refractory CRSwNP, Gevaert et al., demonstrated long-lasting improvement in subjective olfactory function after treatment with mepolizumab. However, this improvement did not reach statistical significance compared with controls, and no psychophysical testing was performed [542]. In 2021, Han and colleagues reported data from the multicentre phase 3 trial SYNAPSE [543]. In patients with recurrent, refractory, severe, bilateral nasal polyposis (treatment arm n=206, placebo arm n=201), there was a statistically significant improvement in VAS-smell although the change was likely not clinically significant, but not in SIT-40 score between treatment groups. Of note, however, SIT-40 testing was only performed in a small subgroup of n=54 per treatment arm.

Benralizumab is an anti-IL-5Rα monoclonal antibody that causes increased antibody-dependent cellular cytotoxicity of eosinophils and basophils, resulting in near complete depletion of the former cell group. Phase 3 work in patients with corticosteroid/surgery refractive, severe CRSwNP (treatment n=207, placebo n=206) demonstrated significantly improved subjective patient reported smell loss at week 40 in the treatment arm. However, this was not accompanied by significantly improved psychophysical (SIT-40) scores [544].

A number of studies have compared biologic activity with respect to primary and secondary outcomes. Using network meta-analytic methods, both Wu et al., and Oykhman et al., demonstrated dupilumab to be the most effective in improving olfactory outcomes, compared with omalizumab and mepolizumab or omalizumab, mepolizumab and benralizumab, respectively [545,546]. Indirect treatment comparison using the Bucher method has also demonstrated superiority of dupilumab over omalizumab [547]. In a real-world study of dupilumab or omalizumab for severe CRSwNP, two thirds of patients improved after 6 months. Whilst there was no significant difference in scores between the 2 treatment groups, there was a non-statistically significant tendency for olfactory scores to be better with dupi-

Table 8. Summary of current evidence for olfactory training.

Author	Year	Study Type	Study Population; n	Results
			Olfactory Training	
Kattar et al. [403]	2021	Systematic review and meta-analysis	Patients with post-infectious olfactory dysfunction, n=1,047	OT had greater odds of achieving the minimal clinically important difference than controls
Saatci et al. [587]	2020	Prospective	Patients with post-infectious olfactory dysfunction; n=60	OT ball provides better adherence to training process, which is associated with better olfactory outcomes
Al Ain et al. [462]	2019	Prospective	Healthy population; n=36	Those who underwent OT had improved general olfactory function (especially odour identification), and showed increased cortical thickness in the olfactory processing areas of the brain
Jiang et al. [578]	2019	Prospective, controlled	Patients with post-traumatic olfactory dysfunction; n=90	Significant improvement in PEA threshold after 6 months of training, but no significant difference in threshold between 4-odour OT and PEA-only OT groups
Pellegrino et al. [695]	2019	Prospective	Patients with post-traumatic olfactory dysfunction; n=42	There were no changes in OB volumes, improvement in olfactory performance after OT seems to be driven, at least in part, by central rather than peripheral processes
Hummel et al. [589]	2018	Prospective	Patients with post-infectious and idiopathic olfactory dysfunction; n=65	EOG responses to PEA and H2S were recorded more frequently in patients after a course of standard OT
Langdon et al. [576]	2018	Prospective	Post-traumatic olfactory dysfunction; n=42	Statistically significant improvement in group mean n-butanol threshold levels after 12 weeks, but was not sustained at 24 weeks
Oleszkiewicz et al. [585]	2018	Prospective	Patients with post-infectious or idiopathic olfactory dysfunction; n=108	Complexity of OT with regard to odour mixtures or alteration of odour type did not affect benefit from OT
Jiang et al. [577]	2017	Prospective, controlled	Patients with post-traumatic olfactory dysfunction; n=81	No significant treatment effect on SIT-40 scores
Patel et al. [586]	2017	Prospective, controlled	Patients with post-infectious and idiopathic olfactory loss; n=43	Allowing patients to use random concentrations of essential oils to perform OT is as effective as published data using controlled concentrations of odourants
Poletti et al. [584]	2017	Prospective	Patients with post-traumatic and post-viral olfactory loss, n=96	With the exception of threshold scores in post-viral olfactory loss, there were no significant differences between light weight and heavy weight molecule groups
Sorokowska et al. [696]	2017	Meta-analysis	Patients with olfactory dysfunction of mixed causes; n=788-1005 (analysis was done for each "Sniffin' Sticks" subtest separately	Positive and statistically significant effect of OT with large effects on identification, discrimination, and TDI score
Konstantinidis et al. [697]	2016	Prospective, controlled	Post-infectious olfactory loss; n=111	Both short (16 weeks) and long term (56 weeks) training produced significantly improved olfactory function compared with control - with long term significantly better than short
Negoias et al. [590]	2016	Prospective, controlled	Healthy participants; n=97	Unilateral OT produced significant increase in bilateral OB volume
Pekala et al. [582]	2016	Systematic review and meta-analysis	Patients with olfactory dysfunction of mixed causes; n=639	OT may be an effective intervention for patients with olfactory dysfunction, including post-infectious, post-traumatic, and Parkinson's disease
Altundag et al. [573]	2015	Prospective, controlled	Post-infectious olfactory loss; n=85	Longer OT with change of odour was effective for odour discrimination and identification
Kollndorfer et al. [593]	2015	Prospective, controlled	Patients with anosmia and healthy controls, no information on aetiology of olfactory loss; n=24	Sensitivity to detect odours significantly increased in the anosmic group, also manifested in modifications of functional connectivity of olfactory, somatosensory, and integrative networks on MRI
Mori et al. [698]	2015	Prospective, controlled	Healthy children (aged 9-15 years); n=72	Improved threshold and identification in training group compared with non-training
Damm et al. [572]	2014	Prospective, controlled	Patients with post-infectious olfactory loss; n=144	OT was significantly more effective with high concentration of odours and dysfunction <12 months
Geißler et al. [571]	2014	Prospective	Patients with post-infectious olfactory loss; n=39	Longer duration of (≥32 weeks) increased effectiveness of training
Haehner et al. [580]	2013	Prospective, controlled	Patients with Parkinson's disease; n=70	Significant increase in olfactory function
Konstantinidis et al. [575]	2013	Prospective, controlled	Post-traumatic and post-infectious olfactory loss; n=119	Significant improvement in post-traumatic and post-infectious groups
Fleiner et al. [520]	2012	Retrospective	Olfactory loss of differing aetiologies; n=46	Improvement of olfaction
Hummel et al. [570]	2009	Prospective, controlled	Patients with olfactory dysfunction excluding sinonasal disease; n=56	Improvement of olfactory sensitivity
Wang et al. [569]	2004	Prospective, controlled	Patients anosmic to androstenone; n=33	Increased sensitivity following repeated exposure

lumab (p=0.094) [548]. In another study of 'real-life' biologic use for severe asthma in patients with CRSwNP, there was no significant difference between omalizumab, mepolizumab, benralizumab, or reslizumab in terms of olfactory outcomes [549].

Recommendations:

➢ Further research with larger patient cohorts and use of thorough psychophysical olfactory testing is required to fully delineate the effect of monoclonal antibody treatment for CRS-related olfactory dysfunction.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.4)

➢ In severe CRSwNP, biologic treatment appears to improve olfactory dysfunction. Among them, dupilumab seems to be the most effective. However, we would refer you to existing guidelines on the treatment of CRS for use of these medications.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.6)

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors are theorised to improve olfactory function through preventing degradation of intracellular cAMP (see section on, '**Anatomy and Physiology of Olfaction**'), and have been shown to reduce intranasal mucus IL-10 and increase intranasal mucus sonic hedgehog, in parallel with improved olfactory function [550,551].

Two studies in 2009 demonstrated improved olfactory function following phosphodiesterase inhibitor administration. The first of these was a prospective study which assessed Sniffin' Sticks scores before and after administration of pentoxifylline (which was in this case being given for otological conditions) [552]. The authors demonstrated a significant improvement in odour threshold levels, in keeping with a theorised improvement in peripheral olfactory function. However, a mixture of normosmic and impaired patients were included in this study and there was heterogeneity in the route of pentoxifylline administration. The second study by Henkin and colleagues utilised an unblinded controlled trial design to assess the effect of oral theophylline on olfactory function in hyposmic patients with reduced nasal/saliva cyclic adenosine monophosphate (cAMP)/cyclic guanosine monophosphate (cGMP) levels [553]. Whilst this study also demonstrated improved olfactory function with treatment, the patient population (i.e., those with low cAMP/cGMP levels) and study design (an increasing dose of theophylline was given where response was deemed suboptimal – a design which may have neglected spontaneous recovery) limits the generalisability of the results. Furthermore, high doses of theophylline may lead to potential side effects. Possibly with this in mind, in 2012, Henkin and colleagues extended this work by piloting intranasal theophylline in 10 patients who had undergone systemic treatment in their 2009 study [554]. They demonstrated olfactory improvement in a greater proportion of patients after 4 weeks of treatment with intranasal theophylline (8/10) than had improved with 2 to 12 months of oral treatment (6/10). The generalisability of this work is, however, again limited due to patient selection as described above, and lack of control group. Another small pilot study of intranasal theophylline in 8 patients with was presented by Goldstein and colleagues in 2017 [555]. They demonstrated psychophysical (SIT-40) and subjective (Monell-Jefferson Taste and Smell Questionnaire) olfactory improvement in 2 patients and psychophysical or subjective improvement in 2 patients. No information was provided regarding aetiology of OD. Again, there was no control group.

In 2021, Lee and colleagues performed a double-blind, placebo-controlled, randomised controlled trial comparing intranasal theophylline irrigation (n=12) with placebo (saline irrigation, n=10) for the treatment of patients with PIOD [556]. There were no clinically or statistically significant differences in SIT-40 scores following 6 weeks of treatment/placebo. The authors, however, demonstrated a significant improvement in olfaction-related quality of life in the treatment group using the QOD-NS. There was no clinically meaningful change in another QOL PROM used in the study, the Olfactory Dysfunction Outcomes Ratings (ODOR) questionnaire. Following on from this, a phase 2, triple-blinded, placebo-controlled RCT (SCENT2) was performed in patients with C19OD [557]. Whilst there was some degree of subjective and psychophysical (SIT-40) improvement with 6-weeks saline irrigation + theophylline (n=26), compared with saline alone (n=25), these differences did not reach statistical significance. Further trials are currently ongoing.

Disappointing results have been demonstrated following double-blind administration of sildenafil (a cGMP type 5 phosphodiesterase inhibitor) [558] and caffeine [559], and in a small case series of pentoxifylline use [560]. Finally, application of topical theophylline to supravital mouse olfactory epithelium, did not lead to enhancement of associated EOG recordings [561].

Recommendation:

➢ Currently, there is insufficient clinical evidence to support the use of phosphodiesterase inhibitors in the treatment of olfactory dysfunction for any underlying aetiology.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.5)

Intranasal calcium buffers

Free calcium within the nasal mucus layer plays a role in negative feedback of the intracellular olfactory signalling cascade [562,563]. It is therefore theorised that sequestration of free calcium, using buffer solutions such as sodium citrate, may lead to amplification of the olfactory signal and consequent improvement in olfactory function.

In 2005, Panagiotopoulos and colleagues reported improved odour identification scores in hyposmic patients treated with intranasal sodium citrate [564]. Whilst subgroup analysis according to aetiology was not undertaken in this study, it is worth noting that the majority of these patients had post-infectious hyposmia. Using a single-blind, placebo-controlled study design, Whitcroft et al. also demonstrated an improvement in the odour identification scores of patients with PIOD, following a single administration of intranasal sodium citrate [565]. Similarly, Philpott and colleagues performed a double-blind, placebo-controlled

trial of one-time sodium citrate treatment compared with sterile water, in patients with OD of mixed causes [566]. They demonstrated improved threshold scores in the treatment group (n=31) compared to controls (n=24) for three out of four odours tested. A further, prospective and internally controlled study in PIOD patients showed significantly improved composite threshold and identification scores after one-time intranasal sodium citrate treatment [567]. This group additionally investigated the effect of prolonged sodium citrate treatment in 60 patients with PIOD [568]. Patients applied sodium citrate drops to the right nasal cavity in the Kaiteki position, twice a day for 2 weeks. The left nasal cavity was untreated and, therefore, served as an internal control. Monorhinal "Sniffin' Sticks" testing at the end of the study period demonstrated no statistically or clinically significant treatment effect on quantitative olfactory function, when comparing treated and untreated sides. However, when taking the best monorhinal score from each side, there was a statistically significant improvement in composite TDI scores at the end of the study. Additionally, there was a significant reduction (82%) in the proportion of patients reporting phantosmia (but not parosmia). Given these improvements over a relatively short study time, it would be of interest to extend this work – particularly with respect to qualitative OD, for which there are few available treatments.

Recommendation:

➢ Currently, there is insufficient clinical evidence to support the use of calcium buffers, in the treatment of olfactory dysfunction for any underlying aetiology.

o Delphi result: Agreed (score 7-9 = 94%, average score 8.5)

Olfactory training (OT)

It is known that repeated exposure to androstenone can improve olfactory sensitivity to this odour(569). This principle underlies OT, in which patients are treated through repeat and deliberate sniffing of a set of diverse odourants over a period of at least 3 months.

In 2009, Hummel and colleagues prospectively investigated the utility of such training in a group of patients with olfactory loss due to PIOD, PTOD or idiopathic aetiologies. Forty of these patients underwent twice-daily smell training using 4 odourants: phenyl ethyl alcohol 'PEA' (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves). Compared with baseline psychophysical olfactory test scores (using Sniffin' Sticks), the training group significantly improved at 12 weeks, whereas the non-training group (n=16) did not [570].

Since this time, increasing evidence has demonstrated the benefit of OT in PIOD. In 2014, Geißler et al. [571], demonstrated improved psychophysical test scores following prolonged training (32 weeks) (however, these results are limited by lack of a comparative control group). A randomised, controlled, multicentre study led by Damm et al. in 144 patients also recently showed that OT with high odour concentrations resulted in greater improvement than very low odour concentrations [572] indicating that OT is, in fact, not related to sniffing but to olfactory stimulation; this study was also the first 'quasi placebo'-controlled study demonstrating the efficacy of OT. Altundag and colleagues also showed improved olfactory function following OT for 9 months (using 4 different odours every 3 months – so called 'modified OT'), with greater benefit being seen following longer training duration [573]. A recent systematic review and meta-analysis of OT specifically for PIOD demonstrated that patients receiving OT had greater odds of achieving the minimal clinically important difference (for all studies included, increase in TDI > 6) than controls (odds ratio 2.77, 95% CI 1.67-4.58) [403]. There have been multiple studies specifically addressing the effect of OT in C19OD, often in combination with some form of intranasal or systemic medication, and using varying subjective or psychophysical outcome measures. Hwang et al., recently performed a systematic review and meta-analysis of OT in C19OD, including 9 studies and 823 patients, all of whom had C19OD for at least 2 weeks [574]. Across all participants, they demonstrated significantly improved standardised 'olfactory score' and 'olfactory dysfunction rate' after OT. Subgroup analysis according to disease duration (acute <30 days, chronic >30 days) was also performed. Whilst there was improvement in both groups, the olfactory score after OT was significantly higher in the acute group. Whilst this may in part be due to increased efficacy with early intervention, there may also be some degree of confounding caused by greater levels of spontaneous recovery in the acute group. Subgroup analysis was also performed according to the duration of OT – no significant difference was demonstration where training programmes of less or more than 8 weeks were used.

With regards to PTOD, results of OT are more heterogenous. In 2013, Konstantinidis and colleagues demonstrated clinically significant improvement in a greater proportion of PTOD who had performed OT, than non-OT controls [575]. However, post hoc analysis of the published results shows that this improvement (33% of 38 patients vs 13% of 15 controls) did not reach statistical significance (p=0.12). Langdon and colleagues performed a prospective randomised controlled trial in 42 patients with PTOD [576]. Compared with controls, they demonstrated statistically significant improvement in group mean n-butanol threshold levels after 12 weeks, but this was not sustained at 24 weeks. In terms of clinical improvement (defined as a 30% increase in n-butanol threshold test score from baseline) – 26% of OT patients and 5% of non-OT patients achieved clinical improvement (n=21 in each group). Again, post hoc analysis of published results demonstrates that this was a statistically

significant result (p=0.03). There were no statistically significant improvements in group mean Barcelona Smell Test (BAST-24) or VAS ratings. Jiang and colleagues reported two studies in 2017 and 2019 addressing the effect of OT on patients with PTOD. In the first of these studies, the authors demonstrated a significantly higher proportion of patients achieving improved PEA thresholds in the training group (n=42, training with PEA only) than in the control group (n=39, training with mineral oil) [577]. However, there was no significant treatment effect on SIT-40 scores (Traditional Chinese version: 'UPSIT-TC'). In 2019, Jiang and colleagues performed a further randomised trial comparing standard 4-odour OT with PEA only OT (n=45 in each group) [578]. They demonstrated significant improvement in PEA threshold after 6 months of training in both groups, but no significant difference between groups. UPSIT-TC score improved significantly in the PEA-OT group, but not the 4-odour OT group. Of note, patients in both of these studies had been pre-treated with prednisolone and zinc. Finally, it has been suggested that OT may lead to differences in functional MRI activity in PTOD [579]. In general, patients with PIOD seem to benefit to a greater extent than PTOD patients. This may be due to underlying diversity in the severity of traumatic brain injuries and/or some greater pathophysiological barrier to OT-induced perceptual plasticity in this group.

The benefit of OT has also been demonstrated in patients with neurodegenerative disease [580]. Few studies, however, have addressed the effect of training in patients with sinonasal disease [520,581] [for a list of studies see Table 8; for 2 meta-analyses of OT in mixed patient cohorts see [582,583]].

Further work in mixed patient cohorts has demonstrated no difference in outcomes using OT with high vs. low molecular weight odours [584], single molecule odours vs aromas vs sequentially alternating odours [585] or use of self-purchased essential oils (with therefore uncontrolled concentrations) vs clinician provided odours [586]. The use of administration adjuncts such as the 'olfactory training ball' (an ergonomic foam ball used for odour presentation) has been shown to confer some benefit over standard OT in PIOD patients [587].

The exact underlying mechanism for improvement following smell training is unknown. However, evidence suggests some degree of plasticity both at peripheral and central levels. In rats, there is increased electrophysiological activity at the level of the OE following training in an odour identification task [588]. Similarly, in humans, EOG responses to PEA and H2S were recorded more frequently in patients (PIOD and idiopathic OD) following a course of standard OT, suggesting either some modification at the level of the OR (e.g. upregulation), or increase in functional OSN population [589]. Increased OB volume has also been demonstrated in healthy participants after a period of OT (interestingly, there were increases in bilateral OB volume despite monorhinal OT) [590]. Following excitotoxic OB ablation in rats, OT has been associated with increased subventricular zone neurogenesis and OB dopaminergic interneurons [229,591]. Structural changes in grey matter volume and cortical thickness upstream of the OB have also been demonstrated after OT in humans [592]. Finally, OT appears to cause alterations in functional connectivity [593].

Given the low associated cost and established safety profile of OT, it is an attractive treatment modality, which can be employed with relative impunity.

Recommendation:

➢ Olfactory training can be recommended in patients with olfactory loss due to several aetiologies, such as PTOD and PIOD. However, this treatment requires further evaluation in patients with sinonasal inflammatory disease and neurodegenerative diseases.

o Delphi result: Agreed (score 7-9 = 98%, average score 8.7)

Surgery

Surgical intervention is largely reserved for treatment of patients with CRS with or without polyps, with superior outcomes generally demonstrated in patients with polyps [594]. Similar to corticosteroid treatment, extensive guidelines exist for the use of surgery in such patients [85,192,193,595]. Cochrane reviews have been published regarding the utility of surgery for these patients, though olfaction is not extensively discussed as an outcome [596,597]. However, a meta-analysis of studies assessing olfaction in functional endoscopic sinus surgery (FESS) concluded that such surgery for CRS improves 'nearly all' subjective and psychophysical measures of olfaction [594]. Furthermore, objective differences in olfactory eloquent grey matter volume and corresponding functional activity has been shown in association with improved olfactory function after FESS in patients with CRS [101,102]. Finally, several previous studies have specifically compared surgical versus medical therapy in CRS with respect to olfactory outcomes [598]. In their multi-centre non-randomised trial of 280 participants, DeConde et al., demonstrated significant improvement in BSIT scores after both surgery or medical therapy (mixed type), but with no statistically significant difference between treatment groups (including during subgroup analysis according to polyp status) [599]. Bogdanov et al., also demonstrated comparable olfactory improvement (subjective and Sniffin' Sticks TDI score) after treatment of CRSwNP with systemic corticosteroids or FESS, in their prospective cohort of 52 patients [491]. Conversely, Baradaranfar and colleagues demonstrated superior olfactory outcomes (subjective 10-point scale and CCCRC) in CRSwNP patients (total n=60) receiving intranasal corticosteroids + FESS compared with those receiving intranasal corticosteroids alone,

Table 9. Summary of current evidence regarding the utility of surgery in olfactory dysfunction (adapted from ref [716]). Evidence regarding surgery for CRS has not been included as this has been extensively described elsewhere (e.g. [85]).

Author	Year	Study Type	Treatment Method	Study Population; n	Results
			Surgery		
Besser et al. [606]	2021	Prospective	Septo±rhinoplasty, or ESS	Patients for nasal surgery; n=65	Olfactory function did not improve overall after 3 months in 50% of patients
Pfaff et al. [607]	2021	Systematic review and meta-analysis	Septoplasty, Septorhinoplasty, Rhinoplasty	Patients undergoing nasal surgery; 25 included studies; n=1721	Transient decrease in olfaction immediately after surgery, followed by significant improvements in olfaction (p<0.001)
Whitcroft et al. [102]	2021	Prospective cohort	Endoscopic sinus surgery	Patients with CRS, healthy controls; n=41	Functionally significant structural plasticity within the primary and secondary olfactory cortices in patients 3 months after surgery, increased psychophysical scores
Elbistanli et al. [605]	2019	Prospective	Open septoplasty, Rhinoplasty + lateral osteotomy, Septorhinoplasty + medial and lateral osteotomy	Patients undergoing septorhinoplasty; n=60	Significantly decreased CCCRCT, Butanol threshold and smell identification scores among those who had medial osteotomy at 1 month after surgery, but improving at 4 months post-op
Whitcroft et al. [101]	2018	Prospective	Endoscopic sinus surgery	Patients with CRS; n=12	Improved olfactory function at 3 months post-surgery for CRS was associated with increased post-operative grey matter volumes within the primary and secondary olfactory networks
Hanci et al. [609]	2016	Prospective	Laparoscopic sleeve gastrectomy	Morbidly obese patients with smell disorder; n=54	Significant improvement of TDI scores in obese patients after surgery
Kohli et al. [594]	2016	Meta-analysis	Endoscopic sinus surgery	Patients with CRS; 31 studies; n=3,756	ESS improves subjective and objective measures of olfaction in CRS, with greater improvement in those with nasal polyps and preoperative olfactory dysfunction
Morrissey et al. [336]	2016	Retrospective	Surgical resection of olfactory neuroepithelium	Patients with peripheral phantosmia; n=3	Resolution of phantosmia
Randhawa et al. [603]	2016	Prospective	Septorhinoplasty	Patients undergoing septorhinoplasty; n=43	Significant increase in the 12-item 'Sniffin' Sticks' Screening test after septorhinoplasty (p<0.001), but no proven clinical benefit
Ulusoy et al. [604]	2016	Prospective	Spreader grafts in Septorhinoplasty	Patients for open septorhinoplasty; n=68	Superior widening effect of spreader grafts over the nasal valve and significantly higher post-operative TDI scores in patients with spreader grafts
Altun & Hanci [699]	2015	Prospective	Nasal septal perforation repair	Patients with septal perforation and smell disorder; n=42	Statistically significant improvement in TDI scores with successful closure of defect (p,0.001); closure success in 92.8%
Holinski et al. [700]	2015	Prospective	Roux-en-Y gastric bypass	Highly obese patients with hyposmia; n=10	Significant increase in TDI scores in obese patients 6 months after surgery (p=0.011), mainly due to odour discrimination (p=0.01)
Kuperan et al. [701]	2015	Prospective, controlled	Endoscopic olfactory cleft polyp removal	Patients with CRSwNP in the olfactory cleft; n=17	Significantly greater increase in SIT-40 scores in those who underwent olfactory cleft polyp removal (p<0.00932)
Poirrier et al. [602]	2013	Prospective case series	Septorhinoplasty	Patients for septorhinoplasty; n=76	Septorhinoplasty was effective at addressing nasal obstruction, discharge, olfaction, related sleep disturbance, and emotional symptoms
Razmpa et al. [376]	2013	Prospective	Aesthetic septorhinoplasty	Patients with normal olfaction and nasal function; n=102	No significant change in odour identification scores post-operatively
Schriever et al. [601]	2013	Prospective	Nasal sinus or nasal septum surgery	Patients with nasal or sinonasal complaints; n=157	Olfactory function improved significantly 3.5 months after surgery in patients who received nasal sinus surgery, No significant increase in patients who underwent nasal septum surgery
Poirrier et al. [602]	2012	Prospective case series	Septorhinoplasty	Patients undergoing functional and reconstructive septorhinoplasty; n=76	Significant improvement in sense of smell/taste (based on 1 item from SNOT-22) among those who underwent Septorhinoplasty
Richardson et al. [608]	2012	Prospective	Gastric bypass surgery	Morbidly obese patients; n=95	Gastric bypass patients were more likely to have olfactory dysfunction pre-operatively than controls, but function was not affected by surgery
Pade et al. [88]	2008	Prospective	Septoplasty ± reduction of turbinates	All patients listed for nasal septal/turbinate surgery; n=150	At mean 4 months post op: 13% improved function, 81% stable function, 7% deterioration in function
Philpott et al. [350]	2008	Prospective	Rhinologic surgery	Patients with rhinological complaints; n=80	Post-operative combined olfactory test scores showed significant improvement (p = 0.02) with post-septoplasty patients showing the most significant improvement (p = 0.001)
Alobid et al. [702]	2005	Prospective	Endoscopic sinus surgery	Patients with nasal polyposis; n=109	Improvement of nasal obstruction and the sense of smell were higher in patients treated with ESS than in patients treated only with steroids at 6 months but not 12 months after surgery
Jankowski et al. [487]	2003	Prospective	Radical ethmoidectomy with middle turbinate resection	Patients with nasal polyps; n=32	Increased post-operative subjective olfactory function that remained stable up to 12 months post-op
Leopold [14]	2002	Retrospective case series	Intranasal removal of olfactory epithelium	Patients with phantosmia; n=18	Resolution of phantosmia in all but one patient
Lildholdt et al. [703]	1997	Prospective	Polypectomy, systemic steroids	Patients with nasal polyposis, n=124	No statistical difference in olfactory test scores between any treatment groups
Kimmelman [704]	1994	Prospective	Septoplasty, Open and closed nasal bone reduction, Rhinoplasty, Ethmoidectomy, Nasal polypectomy, Caldwell-Luc procedure	Patients who underwent various types of nasal surgery; n=93	Those who underwent ethmoidectomy and polypectomy had significantly lower mean SIT-40 scores postoperatively (p<0.05) compared to other surgery types, but a general improvement in post-operative scores was observed (p=0.029)
Leopold et al. [705]	1991	Prospective case report	Intranasal removal of olfactory epithelium	Patient with unilateral phantosmia; n=1	Resolution of phantosmia and return of olfactory function

Author	Year	Study Type	Treatment Method	Study Population; n	Results
Lildholdt et al. [706]	1988	Prospective	Polypectomy, systemic steroids	Patients with nasal polyposis; n=53	Significantly higher proportion of patients expressing intact smell after 2 weeks of medical than surgical treatment, with no significant difference between groups at 2-12 months after
Stevens et al. [707]	1985	Prospective	Nasal surgery	Patients undergoing nasal surgery (differing aetiologies); n=100	Similar numbers of improved olfaction and no change in olfaction

at 12 weeks [600]. Again, however, we would refer you to current guidelines for the management of CRS when considering possible treatment options.

The utility of surgery in addressing OD due to causes other than CRS is less well established. In a follow up study, Schriever and colleagues demonstrated that nasal septoplasty had no beneficial effects on olfaction as measured at one year [601], though other studies have demonstrated benefit [350]. The effect of septorhinoplasty on olfaction has not yet been sufficiently demonstrated, though some reports suggest that it may lead to improved function, possibly through modification of the internal nasal valve and consequent airflow and odorant delivery to the OCs [602–607]. Dilatation of the OC has been reported to be beneficial in terms of olfactory function [487]. Surgery other than nasal surgery, e.g. gastric bypass does not seem to improve olfactory function [608], though there is controversy in the literature [609]. It should also be noted that there is a small risk of worsening olfactory function after sinonasal surgery [610].

Recommendations:

- ➢ Functional endoscopic sinus surgery for olfactory loss caused by the chronic rhinosinusitis disease spectrum should be undertaken in line with existing guidelines, and is not recommended for olfactory dysfunction without associated chronic rhinosinusitis.
  - o Delphi result: Agreed (score 7-9 = 96%, average score 8.6)
- ➢ There is presently insufficient evidence to support other surgery types for olfactory dysfunction.
  - o Delphi result: Agreed (score 7-9 = 100%, average score 8.7)

Treatment of Qualitative Olfactory Dysfunction

The evidence base for treatment of qualitative OD is particularly weak [7]. This is in part because the majority of studies addressing the treatment of OD have quantitative primary outcome measures and are therefore not designed to rigorously assess qualitative treatment effect. Additionally, in the case of phantosmia, the relative rarity of the condition and its varied underlying aetiologies make it difficult to study or generalise data across studies.

Parosmia

Given the frequent association of parosmia with quantitative OD, its treatment is often considered as a secondary outcome measure in studies primarily addressing these quantitative conditions (e.g., PIOD).

In a non-randomised multicentre European trial of oral and intranasal corticosteroid use in C19OD, there were significantly fewer patients reporting parosmia after treatment with olfactory training (OT) + oral corticosteroids (27% of n=59) than OT alone (59% of n=71) [611]. However, no pre-treatment baseline data on the presence of parosmia in the different treatment groups were presented, and assessment of parosmia was performed at different time points for these different groups, limiting interpretation of the results. In their 2004 study, Heilmann and colleagues demonstrated reductions in the proportions of patients reporting parosmia (with OD of mixed causes) after treatment with intranasal (3 pre-treatment, 1 post-treatment, n=37) and oral corticosteroids (6 pre-treatment, 1 post-treatment, n=55) [519]. Though not reported in the original study, neither of these reductions reached statistical significance (Fisher's Exact, p=0.62 and p=0.11 respectively), which may possibly be due to a small sample size.

In an unblinded prospective clinical trial, Hummel and colleagues reported a reduction in the proportion of PIOD patients reporting parosmia (48% pre-treatment, 22% post-treatment, n=23) after treatment with oral alpha-lipoic acid (mean duration 4.5 months) [612]. Though not reported in the original study, this reduction did not reach statistical significance (Fisher's Exact, p=0.12). Again, this may possibly be due to a small sample size. As outlined above, there was a non-statistically significant reduction in the proportion of patients reporting parosmia, after treatment of PIOD with sodium citrate [568]. In a recent case series by Garcia and colleagues, 8 out of 9 patients treated with gabapentin [titrated dose with at least three weeks at maximum tolerated dose (range 200mg daily to 300mg twice daily)] for C19OD related parosmia reported subjective improvement ('significant' in 6 out of 9). Patients were additionally treated with daily budesonide rinses and OT. Post treatment quantitative psychophysical scores (SIT-40) were available in 3 patients, all of whom reported significant improvement in parosmia with gabapentin, but showed 'no or minimal improvement in their scores' [613].

Surgical treatment of long-standing intractable parosmia has also been attempted. Liu and colleagues recently described

a novel technique in which airflow to the OC is obstructed through creation of mucosal adhesions at the anterior and inferior inlets. They further describe a single clinical case in which this procedure was used to alleviate unilateral parosmia, with successful results lasting over a two year follow up period [614].

Recommendations:

➢ A higher level of evidence is required for existing therapies before recommendations regarding their use in the treatment of parosmia can be made.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.6)

➢ Until further evidence is available, treatment of parosmia associated with known quantitative olfactory dysfunction (e.g., PIOD) should be in line with evidence for the quantitative condition.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.5)

Phantosmia

Phantosmia associated with neurological conditions should be treated as for the parent condition and will often dissipate with such treatment. Accordingly, successful use of topiramate, verapamil, nortriptyline, and gabapentin has been described in patients with migraine [615] or in isolated idiopathic phantosmia [616]. Sodium valproate and phenytoin have also been used successfully in two cases of idiopathic phantosmia [617]. In 2016, Morrissey and colleagues described successful treatment with haloperidol in patients with idiopathic central phantosmia (defined by authors as phantosmia that is bilateral, constantly present and which cannot be ameliorated by local anaesthetic or occlusion of the nostrils) [336]. However, it has to be kept in mind that these observations represent small case series. Large-scale well-designed studies assessing the effects of such medications in the treatment of phantosmia (idiopathic or associated with quantitative OD) are needed, particularly given the risk of potential side effects with these agents.

Local treatment of the OE with topical saline has been anecdotally shown to give temporary relief in some patients, and is associated with no serious side effects [14]. Leopold and Hornung demonstrated temporary improvement in 6 patients with idiopathic or PIOD-associated phantosmia (3 normosmic and 3 hypo-/anosmic) following application of cocaine hydrochloride to the OC [618]. This treatment caused subjective complete anosmia in all 6 patients. In 4 patients, phantosmia returned contemporaneously with olfaction, and in 2 there was a delayed return of phantosmia after return of olfaction. As described above, there was a significant reduction in the proportion of patients reporting PIOD-associated phantosmia after treatment with intranasal sodium citrate for 2 weeks (17 prior to treatment, 3 after: 82.4% reduction) [568]. Unlike cocainisation, there was an associated overall increase in quantitative olfactory function during this time. Furthermore, there was also reduction in the proportion of patients reporting parosmia – though this did not reach statistical significance (23 prior to treatment, 15 after). Given the comparatively good side effect profile, and possible impact on both parosmia and quantitative OD, the use of sodium citrate in the treatment of phantosmia should be further explored.

In cases of distressing, intractable phantosmia, surgical removal of the olfactory epithelium [14,336,619] or olfactory bulb [333,334] has been trialled in a few patients, with reported success. However, these procedures have not been validated and are high-risk and should, therefore, be attempted only as a very last resort in an experienced major medical centre. Moreover, it is unclear the duration of effect from surgical excision of the olfactory epithelium, or if modern surgical techniques including coblation and placements of free grafts (autogenous or xenograft) would be beneficial.

Finally, alternative therapies such as repetitive transcranial magnetic stimulation have been trialled for phantosmia, with some success [620].

Recommendations:

➢ Treatment of phantosmia associated with neurological conditions should be undertaken as for the underlying condition, with appropriate specialist guidance.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.8)

➢ For non-neurological phantosmia, a higher level of evidence is required for existing therapies before recommendations for their use can be made.

o Delphi result: Agreed (score 7-9 = 100%, average score 8.8)

➢ Until further evidence is available, treatment of phantosmia associated with known quantitative olfactory dysfunction (e.g., PIOD) should be in line with evidence for the quantitative condition.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.6)

Novel Treatments

The following sections describe novel treatments for OD at various stages of development.

Vitamin A

Vitamin A is a family of fat-soluble retinoids including beta-carotene from plant foods and retinol from animal foods. Oxidation of these precursors leads to production of the biologically active form, retinoic acid (RA), which is a transcription regulator. In line with its role in gene expression, RA is important in tissue development and regeneration [621,622].

Multiple lines of animal evidence suggest that RA signalling is

required for development of the peripheral olfactory system during embryogenesis, as well as its maintenance during adulthood. For example, disruption of RA signalling impairs olfactory embryogenesis in mice [623] and RA receptors are present in the adult murine OE, where such tissues actively produce RA [624]. It is thought that RA contributes to olfactory progenitor cell differentiation, and in so doing, preventing exhaustion of the stem cell supply or accumulation of non-functional immature neurons [625]. In line with this, mature rats with Vitamin A deficiency have OE with increased markers for cell proliferation, but decreased numbers of mature OSN [626]. In vitro, RA promotes OSN neurite (dendrites and axons) growth and thereby maturation [627]. Furthermore, administration of RA has been shown to cause recovery of age-related odour memory deficits in rats, an effect which was abolished by co-administration of an RA-antagonist [628].

In humans, more limited work has been performed, with varying results. In a 1962 case series, Duncan and Briggs reported that systemic vitamin A was beneficial in 48 of 54 patients with anosmia due to various causes, but mostly PIOD and idiopathic OD [629]. However, the interpretation of this work is limited by non-standardised protocols, high dosage (up to 150,000 IU/day), and reliance on subjective olfactory function as main outcome measure. A small uncontrolled study of 33 patients treated with isotretinoin (a synthetic analogue of vitamin A) for acne demonstrated significant improvement in odour identification scores (screening odour identification, Sniffin Sticks) [630]. In 2012, Reden and colleagues performed a double-blind, placebo-controlled, randomised trial in which 52 patients with PIOD (n=19) and PTOD (n=33) were treated with 10,000 IU/day of systemic vitamin A (n=26) or placebo (n=26) for 3 months [631]. Follow up composite TDI testing at 5 months did not demonstrate any significant improvement in the treatment group. The authors speculated that lack of effect may have been due to insufficient dosage. In order to circumvent potential risks associated with high-dose systemic vitamin A, Hummel et al., performed a retrospective cohort analysis of patients with PIOD and PTOD who were treated either with OT alone (12 weeks, n=46) or OT plus 10,000 IU/day intranasal vitamin A (8 weeks, vit A, 12 weeks OT, n=124) [632]. A significantly higher proportion of PIOD patients achieved clinical improvement in the OT + vit A group than in the OT group (37% vs 23%, p=0.03). Furthermore, OT + vit A resulted in significantly improved odour threshold and odour discrimination scores compared with OT alone in PIOD patients, and significantly improved discrimination scores across all patients.

Further placebo-controlled randomised trials are required to fully delineate the effects of intranasal vitamin A on PIOD [633]. Given the role of RA in neurogenesis, it may also be of interest to investigate the role of vitamin A in age-related OD.

Olfactory implants

Electrical stimulation of sensory organs using neuroprostheses is well established in otology, and a dynamically emerging field in ophthalmology. The principle facilitating such prostheses is stereotyped spatial mapping within the target sensory organ. For example, sound frequency is spatially represented within the cochlea, as is the visual field within the retina.

Some degree of 'rhinotopy' has been established in animals, where the OE can be roughly divided into zones (the number of which appears to be species dependent), each with differing OSN expression. Such mapping is reflected in the OB, where axons from OSN expressing the same receptor type synapse within a set number of glomeruli within the ipsilateral OB (again the number being species-dependent). The neural fingerprint of an odour is therefore at least partially spatially encoded – though during normal olfaction in vivo, odourant absorption characteristics and nasal aerodynamics contribute to more complex spatiotemporally determined neural fingerprints [49].

Direct electrical stimulation of the rodent olfactory bulb has been shown to produce spatial patterns of activation in a similar way to those seen with odourant-based OB stimulation [634]. Following on from this work, Coelho and colleagues subsequently demonstrated successful generation of localised field potentials through stimulation of deafferented rat OB using a cochlear implant electrode array [635]. In humans, Holbrook and colleagues electrically stimulated the lateral lamella of the cribriform plate in normosmic patients who had undergone total ethmoidectomy [330]. Subjective smell perception was achieved in 3 of 5 patients tests, though objective evidence through olfactory electroencephalography could not be obtained. Smell perception persisted despite induction of medical anosmia using topical anaesthetic application to the OE; the authors therefore argue the mechanism of perception was through transethmoidal stimulation of the OB, rather than stimulation of the OE. Potential techniques for implant placement have also recently been addressed in a human cadaveric study [636].

Whilst further research is required, the above provides early, but exciting proof of principle for the development of olfactory implant systems, and restoration of olfactory perception in patients with irreversible damage at the level of the OE.

Stem cell therapy

During both homeostatic conditions and following injury, OSN are replaced from a pool of stem cells within the OE [69,637]. This pool is divided into two types: globose stem cells (GBC), pluripotent cells that replace all constituents of the OE under

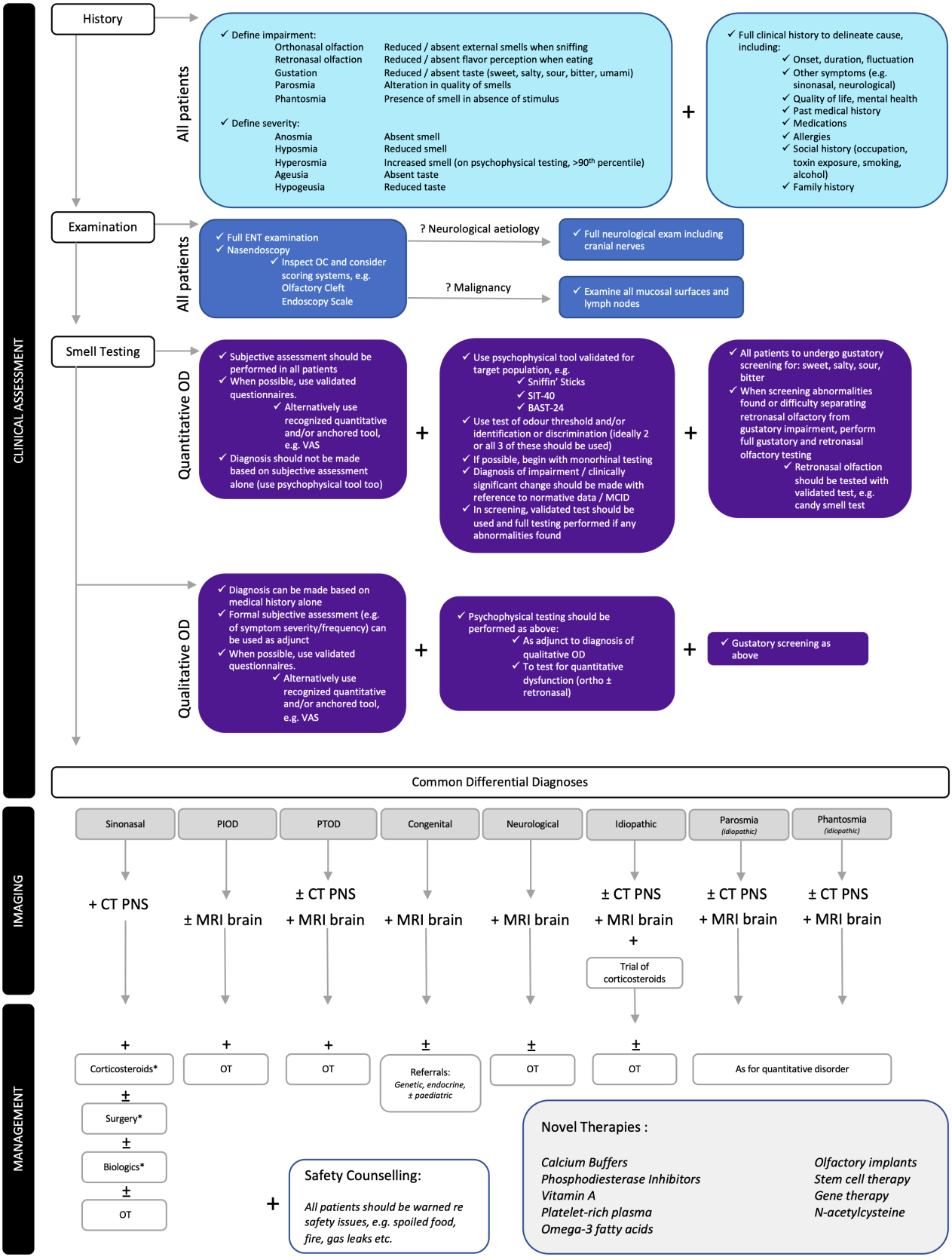

Figure 4. Summary flowchart showing suggested approach to assessment and management of olfactory dysfunction. Please see relevant sections for more detail. *Use according to existing CRS guidelines.

homeostatic circumstances, and horizontal stem cells (HBC), a long-lived mitotically quiescent population that is activated following OSN depletion, for example, during epithelial injury [638,639]. It is thought that impaired neurogenesis may be responsible for OD of various causes, for example, presbyosmia, PIOD and PTOD [229,639]. Reduced neurogenesis may also be implicated in conditions such as CRS [94], where chronic inflammation has been shown in animal models to cause functional shift in HBCs from a neurogenic regenerative to an immune phenotype [95].

Targeting stem cell populations to augment neurogenesis has been trialled in rodents [640–642]. In 2019, Kurtenbach and colleagues described a novel mouse model in which hyposmia could be induced through conditional deletion of a ciliopathy-related gene (Intraflagellar Transport 88, IFT88) [643], so preventing restoration of OSN through endogenous stem cell populations. Intranasal infusion of purified GBCs into these experimentally hyposmic animals resulted in stem cell engraftment and production of mature OSN, that were identified immunohistochemically. The functional status of the resultant OSN was subsequently confirmed using electroolfactography and behavioural (odour avoidance) assays. Transplantation of other stem cell populations has also been attempted – improved behavioural assays and basic histological evidence for OE regeneration was demonstrated by Khademi et al., following intranasal application of adipose-derived mesenchymal stem cells in 3-methylindole-anosmic rats [644].

Continued in vitro and animal work should help to delineate the feasibility of human olfactory stem cell transplantation, as well as identifying pharmacological targets for augmentation of olfactory neurogenesis.

Gene therapy

Gene editing techniques, in particular, viral-based systems, have been used in a limited number of studies to demonstrate improved olfactory function following restoration of ciliary function in animal ciliopathy models [645,646]. Viral-based, CRISPR, or other gene editing systems such as small interfering RNAs, may be of future use, particularly in patients with congenital OD of single gene origin.

Platelet-rich plasma

Platelet-rich plasma (PRP) is an autologous concentrate of platelet-rich plasma protein, produced from a target recipient's whole blood. During haemostasis, activated platelets release a variety of growth factors and cytokines, including platelet derived growth factor, vascular endothelial growth factor, transforming growth factor beta, insulin-like growth factor, interleukin 8, nerve growth factor and others. Collectively these factors promote angiogenesis, cell proliferation, differentiation and survival, ultimately contributing to injury repair and regeneration. On this basis, the therapeutic utility of PRP has been investigated through in vitro and animal models, as well as a heterogeneous body of clinical research spanning several medical and surgical specialties [647].

Of particular interest to olfaction are the purported benefits of PRP in promoting axonogenesis and neurogenesis. In an animal model of Alzheimer Disease, intranasal application of Endoret (a PRP gel preparation) caused activation of neuronal progenitor cells, reduced amyloid-beta induced neurodegeneration and enhanced hippocampal neurogenesis [648]. More specifically, in a murine model of anosmia, post-injury intranasal PRP lavage caused significantly improved behavioural (food finding test times) and basic histological scores compared with control (saline lavage) [649]. A limited number of clinical studies have investigated the utility of PRP application in patients with OD. In 2017, Mavrogeni et al., reported positive results after repeat intranasal injection of PRP into the 'olfactory' area of the nose in 5 patients with refractory, non-CRS 'anosmia', over a three-month period [717]. However, this study is limited by lack of formal psychophysical olfactory testing or control group. In 2020, Yan and colleagues demonstrated significantly improved average TDI score, as well as subjective improvement, at 3 months after one-time PRP injection within the OC of 7 patients with OT + topical corticosteroid-refractory OD [650]. Greatest benefit was found in patients with hyposmia, rather than anosmia, though again, this study lacks an appropriate control group. Yan and colleagues expanded on these findings with a recent RCT investigating intranasal PRP injection (3 x to OC) vs. saline in patients with C19OD (n=26) [651]. They demonstrated a statistically significant improvement in composite TDI score and individual discrimination score in the intervention arm (n=14) vs the placebo arm at 3 months (n=12) (TDI – 3.67 points, 95% CI: 0.05-7.29, p=0.047; D – 2.40 points 95% 0.80- 4.00, p=0.004). They did not, however, demonstrate any significant treatment effect on individual threshold or identification scores, or on subjective olfactory function (VAS). Finally, Klug and colleagues recently presented work in which a PRP-soaked absorbable sponge was applied unilaterally to the OC of treatment resistant anosmics for 3 months, with a saline soaked sponge applied to the contralateral OC, and where lateralisation of active treatment was randomised [652]. Whilst they demonstrated improvement in overall B-SIT scores, there was no significant difference between treatment and control sides. This may be due to some mechanism of bilateral treatment activity, or due to method of topical application used.

Further rigorous study is required, with standardised PRP type and preparation (e.g., use of potentially confounding sodium citrate as anticoagulant), larger patient cohorts and appropriately matched control groups, prior to recommendation for routine clinical use.

Omega-3 fatty acids

Omega-3 fatty acids comprise a group of polyunsaturated fatty acids that are key substrates of lipid metabolism. Three types of omega-3 are important in humans: α-linolenic acid (ALA – an essential fatty acid only obtainable from diet), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Animals fed omega-3 fatty acid deficient diets perform poorly in odour discrimination tasks, compared to controls [653]. This is thought to be due to reduced levels of DHA found within the brain, and specifically the OB. In older adult humans, diets that rich in fish and nuts (both naturally high in omega-3 fatty acids) confer reduced risk of olfactory impairment (as determined through odour identification testing) [654]. Furthermore, a small, randomised, double-blind, placebo-controlled trial demonstrated improved screening odour identification scores (12-item screening Sniffin Sticks) in patients with mild cognitive impairment treated with DHA (n=11), compared with placebo (n=14) [655].

In 2020, Yan and colleagues performed a randomised controlled trial in which patients undergoing endoscopic sellar or parasellar tumour resection were treated post-operatively with either intranasal saline irrigation alone, or saline irrigation + omega-3 supplementation [656]. 87 patients (treatment n=46, control n=41) completed the study period, during which omega-3 supplementation was found to be protective against olfactory loss (Odds Ratio 0.05, p=0.04), according to odour identification testing (SIT-40). The authors speculate that this may be due to anti-inflammatory and neuroprotective treatment effects. More recently, a non-blinded, prospective study in 58 patients by Hernandez et al., suggested that effects of OT were significantly higher when omega-3 was supplemented for 3 months (TDI scores) compared to OT alone [657]. Further research is required to determine whether omega-3 fatty acid supplementation is of benefit in non-iatrogenic or age-related OD.

N-acetylcysteine

N-acetylcysteine (NAC) is a glutathione substrate with antioxidant, anti-inflammatory, anti-thrombotic and neuroprotective properties. Recent work from Goncalves and Goldstein demonstrated reduced OSN loss following surgical bulbectomy in rats treated with NAC, compared with controls [658]. This was accompanied by alterations in oxidative stress pathway gene expression, as demonstrated in olfactory cell cultures. Given the established clinical safety profile of NAC, work is currently underway to establish the utility of this treatment in OD. Furthermore, treatment of COVID-19 patients (in whom glutathione deficiency in combination with increased measures of oxidative stress have been demonstrated [659] with NAC has been undertaken in multiple studies over the course of the pandemic, with varying results. It would be of interest to determine whether olfactory outcomes in such patients were superior to matched patients in whom NAC was not used.

Other treatments

In addition to the above, numerous other treatments have been tried, including but not limited to, palmitoylethanolamide and luteolin [660], acupuncture [661], lavender syrup [662], famotidine [663] blockage of the stellate ganglion [664], a mix of herbal drug (Tokishakuyaku-san) [665,666], B vitamins [667]. They will not be described here in detail, because they await further study.

Please see Figure 4 for summary flowchart showing suggested approach to assessment and management of olfactory dysfunction.

Recommendations:

➢ Further high-quality research is required for all of the above novel treatments before recommendations for their clinical use can be made.

o Delphi result: Agreed (score 7-9 = 96%, average score 8.7)

Recommendations and delphi exercise summary

Each of the 45 recommendations including in this position paper reached agreement during the first round of the modified Delphi exercise (≥70% score 7-9, ≤15% score 1-3). The recommendations are summarized in Table 10. Figure 5 highlights the recommendations with the lowest level of consensus, which will be discussed in the following section.

Though agreed during the first round, recommendation 19 only just achieved consensus: 'Psychophysical olfactory testing should ideally begin with monorhinal odour threshold testing, if feasible. Where there is no significant difference in lateralised scores, testing may continue birhinally.' The major concern surrounding this recommendation was difficulty in achieving the associated prolonged testing times in a busy clinical environment. Anecdotally, monorhinal psychophysical testing only appears to be routinely performed in a select number of specialist clinics, and in such cases, more often under research circumstances. Nevertheless, the additional clinical information provided by monorhinal testing was felt to be sufficiently important by enough of our co-authors, for this recommendation to be agreed as ideal practice.

Recommendations 25 and 26 were concerned with gustatory testing: 25 – 'Comprehensive psychophysical assessment should include gustatory screening for sweet, salty, sour, and bitter tastes in all cases.'; 26 – 'Full gustatory testing should be performed where abnormalities are identified on screening or where it is not possible to differentiate between impaired gustation and retronasal olfaction. Accordingly, this should ideally include discrimination between retronasal olfaction (flavours) and gustatory (taste) abnormalities.' Again, the major concern regarding these recommendations was lack of resources (testing equipment, time and staff) in busy clinical environments. Furthermore, a small number of co-authors felt that there should be clear clinical division between olfactory and gustatory care, and that olfactory assessment should therefore only focus on olfaction. However, again, the importance of full chemosensory testing was felt to be sufficient by the majority of co-authors, and this recommendation was therefore agreed.

Finally, recommendation 27 stated that 'Whilst electrophysiological and imaging studies are often reserved for research purposes, EEG-based olfactory testing can be useful for medico-legal purposes.' Here, there was concern amongst some co-authors that this recommendation could be felt prescriptive – that EEG was required during medico-legal assessment, which would not be possible in centres without the appropriate equipment. However, it should be clarified that EEG 'can be useful' for such purposes but is not a required minimum standard.

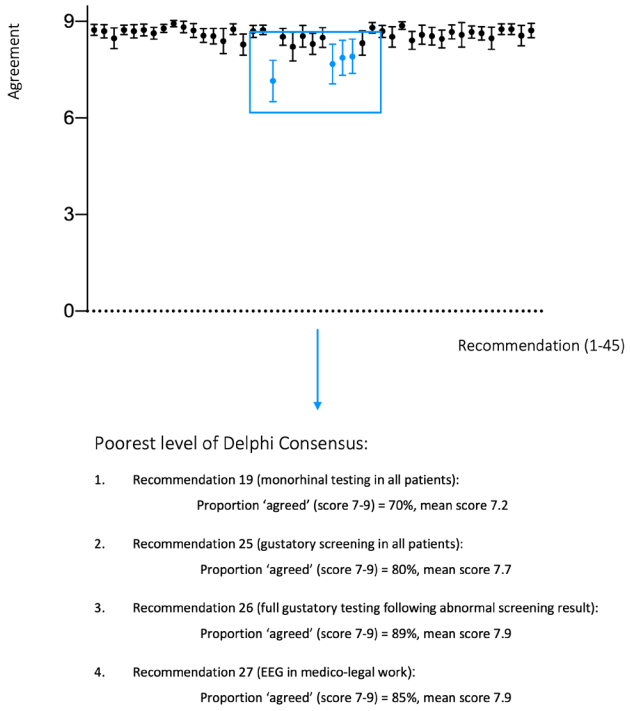

Figure 5. Summary of Delphi Exercise Results (mean and 95% confidence intervals). Highlighted data points = recommendations with poorest level of consensus.

In light of the above, following further discussion and consideration of practical limitations, in addition to newly emergent international literature(443,668,669), the following additional recommendation is made:

Recommendation:

➢ Increased funding should be made available in order to facilitate chemosensory assessment as outlined in this position paper. Where this is not possible at the local level, clear referral pathways should be established to specialist centres where such assessment can be undertaken, thereby enabling equitable access to care.

Table 10. Collated and numbered recommendations.

	Definitions
1	We recommend the use of the terms highlighted in bold in the above table, with their associated definitions.
	Causes and classifications of olfactory dysfunction
2	Classification of olfactory dysfunction should be according to underlying aetiology (e.g. post-infectious, post-traumatic etc)
3	Idiopathic olfactory dysfunction is a diagnosis of exclusion that should only be made following careful assessment, including normal MRI and exclusion of underlying inflammatory pathology.
	Qualitative olfactory dysfunction
4	The presence of parosmia or phantosmia, and their potential underlying causes, should be established through careful medical history.
5	Structured symptom questionnaires, severity scores, and psychophysical olfactory tests may be used as adjuncts to diagnosis.
6	Due to their frequency of co-occurrence, assessment for quantitative olfactory dysfunction should be undertaken when qualitative dysfunction is reported.
7	Imaging in qualitative dysfunction may be of use where there is suspicion of an endogenous odour source, or central pathology.
8	Where a neurological or psychiatric cause is suspected, appropriate specialist input should be sought.
	Clinical assessment
9	Thorough clinical histories should be sought from all patients.
10	Patients with suspected olfactory dysfunction should undergo a full ENT examination, including nasal endoscopy with careful inspection of the olfactory cleft.
11	Basic neurological examination should be undertaken where there is suspicion of an underlying neurological aetiology, or in otherwise assumed idiopathic cases, though formal and detailed neurocognitive testing can be deferred to the appropriate specialists.
12	In patients reporting olfactory dysfunction, subjective olfactory assessment should be undertaken in order to fully determine quality of life and disease burden, as well as the clinical impact of interventions.
13	When possible, validated questionnaires should be used. When this is not possible, a recognised form of assessment, possibly quantitative and/or anchored, such as a visual analogue scale, should be used.
14	Subjective olfactory assessment should not be relied upon in isolation
15	Psychophysical olfactory assessment tools should be reliable and validated for the target population.
16	Psychophysical olfactory assessment tools used in clinical and research settings should include tests of odour threshold, and/or one of odour identification or discrimination. However, we strongly encourage to test olfactory function by including two or three of these subcomponents.
•	Use of other suprathreshold olfactory testing modalities can be considered, where such tests have been validated and have sufficient normative data.
17	When testing olfaction in children, the test should fit the motivation of the child, be culturally appropriate, and validated for the target age.
18	Definitions of olfactory impairment should only be made with reference to normative values for the psychophysical olfactory test being used.
19	Psychophysical olfactory testing should ideally begin with monorhinal odour threshold testing, if feasible. Where there is no significant difference in lateralised scores, testing may continue birhinally.
20	When reporting changes in psychophysical olfactory test scores, improvement or deterioration in olfactory function should be defined according to established clinical correlates and target population for that olfactory test.
21	Screening for abnormal olfactory function in asymptomatic patients should be undertaken using validated psychophysical olfactory tools.
22	Patients with abnormal screening results should undergo full olfactory testing.
23	When formal psychophysical olfactory testing is not possible (for example, in acutely infectious COVID-19 patients), validated home smell tests may be of use.
24	Patients with abnormal results [on home tests] should undergo full olfactory testing.
25	Comprehensive psychophysical assessment should include gustatory screening for sweet, salty, sour, and bitter tastes in all cases.
26	Full gustatory testing should be performed where abnormalities are identified on screening or where it is not possible to differentiate between impaired gustation and retronasal olfaction. Accordingly, this should ideally include discrimination between retronasal olfaction (flavours) and gustatory (taste) abnormalities.
27	Whilst electrophysiological and imaging studies are often reserved for research purposes, EEG-based olfactory testing can be useful for medico-legal purposes.
28	Structural imaging should be undertaken according to suspected underlying aetiology (see table 6). In idiopathic olfactory dysfunction: CT of the paranasal sinuses is optional and may identify inflammation not otherwise diagnosed by endoscopy or trial of corticosteroids; MRI brain is recommended.

	Definitions
29	CT should be performed as first line imaging of the paranasal sinuses when sinonasal inflammation or bony abnormalities are suspected. MRI should be performed as first line when intracranial abnormalities are suspected, or morphometry of the OB is required.
	Treatment of olfactory dysfunction
30	Systemic (short courses) and/or intranasal (long-term) corticosteroids should be prescribed in patients with olfactory dysfunction secondary to CRS, severe allergic rhinitis, and other inflammatory conditions according to existing clinical guidelines.
31	There is limited evidence to support use of systemic or intranasal corticosteroids for other causes of olfactory dysfunction, but if topical steroids are used, a delivery mechanism that can reach the olfactory cleft (i.e. rinses in place of sprays) would be recommended.
32	Potential side effects and contraindications should be taken into account when prescribing systemic corticosteroids.
33	Further research with larger patient cohorts and use of thorough psychophysical olfactory testing is required to fully delineate the effect of monoclonal antibody treatment for CRS-related olfactory dysfunction.
34	In severe CRSwNP, biologic treatment appears to improve olfactory dysfunction. Among them, dupilumab seems to be the most effective. However, we would refer you to existing guidelines on the treatment of CRS for use of these medications.
35	Currently, there is insufficient clinical evidence to support the use of phosphodiesterase inhibitors in the treatment of olfactory dysfunction for any underlying aetiology.
36	Currently, there is insufficient clinical evidence to support the use of calcium buffers, in the treatment of olfactory dysfunction for any underlying aetiology.
37	Olfactory training can be recommended in patients with olfactory loss due to several aetiologies, such as PTOD and PIOD. However, this treatment requires further evaluation in patients with sinonasal inflammatory disease and neurodegenerative diseases.
38	Functional endoscopic sinus surgery for olfactory loss caused by the chronic rhinosinusitis disease spectrum should be undertaken in line with existing guidelines, and is not recommended for olfactory dysfunction without associated chronic rhinosinusitis.
39	There is presently insufficient evidence to support other surgery types for olfactory dysfunction.
	Treatment of qualitative olfactory dysfunction
40	A higher level of evidence is required for existing therapies before recommendations regarding their use in the treatment of parosmia can be made.
41	Until further evidence is available, treatment of parosmia associated with known quantitative olfactory dysfunction (e.g., PIOD) should be in line with evidence for the quantitative condition.
42	Treatment of phantosmia associated with neurological conditions should be undertaken as for the underlying condition, with appropriate specialist guidance.
43	For non-neurological phantosmia, a higher level of evidence is required for existing therapies before recommendations for their use can be made.
44	Until further evidence is available, treatment of phantosmia associated with known quantitative olfactory dysfunction (e.g., PIOD) should be in line with evidence for the quantitative condition.
	Novel treatments
45	Further high-quality research is required for all of the above novel treatments before recommendations for their clinical use can be made.
	Additional Recommendation
[a]46	Increased funding should be made available in order to facilitate chemosensory assessment as outlined in this position paper. Where this is not possible at the local level, clear referral pathways should be established to specialist centres where such assessment can be undertaken, thereby enabling equitable access to care.

Unmet needs and future research

Basic/Translational Laboratory Research

Despite the influence of the pandemic, olfactory research continues to lag behind its special sensory equivalents of hearing and vision. As outlined in some of the previous sections, questions remain regarding several aspects of olfaction. What predisposes patients to PIOD, and why do some pathogens, but not others, cause PIOD? What causes non-syndromic congenital OD? How do we support stem cell regeneration after injury? More generally, our relative ignorance surrounding the pathophysiology of parosmia, for example, reflects gaps in knowledge regarding even more fundamental aspects of how we smell: what defines the odour object, how do we process odour objects and what leads to the distortion of such objects, as is seen in parosmia. To address and ultimately answer these questions requires focused, well-funded basic/lab-based research. Such research would benefit from specific steps, such as the development of immortalised (ideally human) cell lines and organoids, establishing multicentre/international consortia and databases, longitudinal studies, as well as more general shifts in approach, including cross-disciplinary collaboration and training of future sensory scientists.

Clinical Approach

In 2007, McNeill and colleagues performed a survey of UK clinicians and found that, of those who saw patients with OD, 5.4% used chemosensory smell tests routinely, whilst 54.8% did not use any form of such test [670]. More than a decade later, there has been little change. The recent ICAS Study undertook international survey of clinical practice in the assessment of olfactory function and dysfunction [443]. Within the UK, 54.9% of clinicians never used smell tests during the initial assessment of OD as a presenting or isolated symptom, though this proportion fell to 33.3% of those with subspecialty training in rhinology. Outside of the UK (16 primarily European countries), 23.2% of clinicians never tested during this scenario, falling to 7.5% of those with subspecialty training in rhinology. The most commonly cited barriers to routine psychophysical testing were insufficient funding and insufficient time. Using the parallels of vision or hearing, in which diagnosis and treatment decisions would not occur in the absence of psychophysically-proven deficit, routine smell testing should become the standard of care. Only once this has been achieved can diagnoses be accurately made and treatment outcomes accurately assessed. Furthermore, evidence suggests that thorough assessment may help to improve the patient journey, irrespective of available management options or prognosis [140,669].

To help establish psychophysical tests as part of standard clinical care, future research should work to develop tools that are quick and easy to administer and affordable, without sacrificing clinically needed information. Importantly, funding should be provided across different models of healthcare system to enable such testing. Ultimately a standard test should be internationally agreed. Until a time at which such standardisation can be achieved, clear referral pathways to specialist centres should be established, where full chemosensory testing in line with the recommendations contained herein can be performed.

In order to maximise the efficiency of clinical research, international collaboration in the form of registries/databases or multi-centre RCTs should be embraced. In line with this, a core outcomes set for olfactory research has recently been proposed (see: https://www.comet-initiative.org/Studies/Details/1957). Specialist centres such as those described above should be recruited to participate in such data sharing.

Big data work, linking OD with other healthcare outcomes would also be of benefit, but is not possible until disorders of olfaction are appropriately and efficiently coded across different healthcare systems. Furthermore, pan-European and other large scale epidemiological studies are needed, particularly in the wake of the pandemic, to accurately gauge the healthcare and societal burden of OD.

Patient and Participant Involvement

Peer support is particularly important for patients with OD, in whom significant lifestyle modifications may be required, and prognosis may either be poor, or more frequently unknown. The success of charities and organisations such as AbScent, Fifth Sense, Reuksmaakstoornis or STANA, and their associated support groups – with social media providing otherwise difficult to access support during the pandemic – highlight the importance of formal organisation.

Integration of patient voices into all stages of clinical research and service provision planning is paramount. Such voices provide insight into patient journeys, priorities, and may even help to shed light on physiological or pathophysiological olfactory processes. Qualitative, co-produced research addressing patient experience of olfactory dysfunction is therefore important. Ball and colleagues outlined barriers to effective olfactory care [671]. They highlighted the common failure of medical professionals to recognise OD as a problem, as well as issues surrounding inef-

Table 11. A non-exhaustive list of clinical/research priorities in olfaction.

Research Domain	
Biological Understanding	• Pre-clinical models • Olfactory neuroregenerative/neurodegenerative processes • Axonal targeting • Pathophysiological processes for common causes of OD
Clinical Evaluation	• Standardized history • Diagnostic tools for use in qualitative OD • Diagnostic tools for measurement of trigeminal function • Clinical utility of functional neuroimaging for diagnosis
Clinical/Research Networks	• Provision of online toolkit with standardized PROMs and chemosensory testing guidance for use in non-specialist centres • Referral networks to specialist centres where chemosensory testing not available locally • Multicentre collaboration with data input and sharing for high powered research
Biomarker Development	• Olfactory mucus • Olfactory microbiome • In vivo visualization and analysis of olfactory mucosa • Structural/functional brain neuroimaging
Therapeutics	• High quality RCTs in new treatments • High quality RCTs in existing treatments with poor evidence base
Patient and Participant Involvement	• Involvement of patients in setting research agendas and service planning

fective treatments, difficulty in obtaining referrals for specialist care and personal financial burdens. In the UK, the Fifth Sense James Lind Alliance Priority Setting Partnership recently outlined 10 of the top research priorities in smell and taste disorders, following consultation with patients, healthcare professionals and other stakeholders (672).

A non-exhaustive list of clinical/research priorities in olfaction can be found in Table 11.

CONCLUSIONS

In the preceding sections we have provided an overview of current evidence and expert-agreed recommendations for the definition, investigation and management of OD. As for our original Position Paper, we hope that this updated document will encourage clinicians and researchers to adopt a common language, and in so doing, increase the methodological quality, consistency and generalisability of work in this field.

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Authorship contributions

Whitcroft KL: Conceptual design. Writing of manuscript. Production of figures. Integration of co-author comments. Participation in Delphi exercise.
Hummel T: Conceptual design. Supervision of project. Administrative support. Participation in Delphi exercise.
Gane S: Production of figures. Review of content and participation in Delphi exercise.
Hernandez, AK: Editing of manuscript. Integration of co-author comments. Participation in Delphi exercise.
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Conflicts of interest

None relevant.

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