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Post-viral olfactory loss and parosmia

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ABSTRACT

The emergence of SARS-CoV-2 has brought olfactory dysfunction to the forefront of public awareness, because up to half of infected individuals could develop olfactory dysfunction. Loss of smell—which can be partial or total—in itself is debilitating, but the distortion of sense of smell (parosmia) that can occur as a consequence of a viral upper respiratory tract infection (either alongside a reduction in sense of smell or as a solo symptom) can be very distressing for patients. Incidence of olfactory loss after SARS-CoV-2 infection has been estimated by meta-analysis to be around 50%, with more than one in three who will subsequently report parosmia. While early loss of sense of smell is thought to be due to infection of the supporting cells of the olfactory epithelium, the underlying mechanisms of persistant loss and parosmia remain less clear. Depletion of olfactory sensory neurones, chronic inflammatory infiltrates, and downregulation of receptor expression are thought to contribute. There are few effective therapeutic options, so support and olfactory training are essential. Further research is required before strong recommendations can be made to support treatment with steroids, supplements, or interventions applied topically or injected into the olfactory epithelium in terms of improving recovery of quantitative olfactory function. It is not yet known whether these treatments will also achieve comparable improvements in parosmia. This article aims to contextualise parosmia in the setting of post-viral olfactory dysfunction, explore some of the putative molecular mechanisms, and review some of the treatment options available.

Introduction

Olfactory dysfunction can be categorised as being quantitative or qualitative (table 1). Quantitative dysfunction involves alterations in the strength or intensity of perception of odours; while qualitative dysfunction involves distortions (usually negative) to the quality and perception of odours. The two entities can coexist, with up to 60% of all patients with quantitative olfactory dysfunction experiencing some degree of qualitative dysfunction.[1 2]

Sources and selection criteria

We searched PubMed, Cochrane Central Register of Controlled Trials, and Embase using the terms "olfactory dysfunction," "anosmia," and "parosmia" for articles published between 1 January 2010 and 31 December 2022. These articles were reviewed and only those that specifically included patients with post-viral causes were included. We also reviewed reference lists from articles that we deemed to be high quality. Preference was given to randomised controlled trials, meta-analyses, international consensus guidelines, and systematic reviews that have informed these guidelines. We included smaller studies if they were of particular note or if other evidence was unavailable, for example, a case series that specifically included patients with parosmia owing to other available evidence being limited. In general, case reports and small case series were excluded.

Incidence of post-viral olfactory dysfunction

Loss of smell after flu-like infection was first described in 1975.[3] Since then, many reports and series have been published in the literature, and viral infections of the upper respiratory tract are now considered to be one of the most common causes of olfactory dysfunction, accounting for 18-45% of all cases.[4–9] Viruses known to have the capability to induce olfactory dysfunctions include rhinoviruses, coronaviruses, influenza and parainfluenza viruses, enteroviruses, adenoviruses, and Epstein-Barr viruses.[10–12] However, many patients seek assistance long after infection when the causative pathogen can no longer be determined. More recently, SARS-CoV-2 has been identified as a frequent cause of disruption to the sense of smell and has brought new focus to post-viral olfactory dysfunction.[13–15] Incidence of olfactory dysfunction after SARS-CoV-2 infection has been estimated to be 47.9% by a meta-analysis that examined 83 studies of 27 492 patients.[16] This one number fails to explain the variable incidence by geography, sex, SARS-CoV-2 variant, and subtype of olfactory dysfunction. The meta-analysis looked at each of these influences: studies performed in Europe showed a much higher rate of olfactory dysfunction than those in Asia (54.4% *v* 31.4%). Female individuals accounted for most patients—60.4%. Comparative analysis of olfactory dysfunction as caused by four different SARS-CoV-2 subtypes revealed that omicron was associated with fewer cases of olfactory dysfunction than the D614G, alpha, and delta variants.[17]

Estimates of the frequency of parosmia after viral infection before SARS-CoV-2 are limited in the literature. One large Swedish population survey sampled 1713 individuals with questionnaires and structured interview regarding the presence of parosmia, and estimated a prevalence of self-identified parosmia of 3.9%,[9] but the study lacked the ability to determine causality and temporal relation of parosmia to viral infection. The influence of the SARS-CoV-2 pandemic

Table 1 | Quantitative and qualitative dysfunctions

Term	Definition
Hyposmia	Reduced perception of smell, can be specific to one odorant or to all odours
Anosmia	Complete absence of perception of smell; usually trigeminal inputs remain, and some chemically irritating odours may still be perceived
Functional anosmia	Olfactory function is present, but is too poor to be useful in daily life
Parosmia	Distorted perception of odour in the presence of an odorous stimulus
Phantosmia	Perception of odour without an external stimulus

has seen an increase in the published estimates of parosmia—and yet, in the 2021 meta-analysis, the overwhelming contribution of data was from studies of quantitative olfactory dysfunction with only one study of qualitative loss suitable for inclusion. Individual studies that have followed patients with SARS-CoV-2 infection who reported smell loss at the time of acute illness have suggested that 28-43% will have parosmia.[18–20] Notably, many patients continued to have parosmia at six or 12 months.

Identification and quantification of olfactory dysfunction

Time constraints in the clinical environment can limit access to precise measurement of olfactory function, and in practice, we often rely on the patient's response to the question "Have you noticed a change in your sense of smell?" While this first question is reasonable to open discussion, the sensitivity and specificity of an individual's ability to detect loss of smell is variable. The usefulness of screening questions such as "Do you smell odours differently compared with previous experiences?" and "Do you smell odours in absence of an apparent source?" have been examined by Boscolo-Rizzo et al in an observational study of 98 patients[21]; the use of these screening questions suggested a higher prevalence of parosmia than would have been inferred through quantitative olfactory testing alone. In an observational study of 193 patients, Landis et al[22] used a short structured questionnaire that not only indicated the presence or absence of parosmia, but also could be used to derive the severity of parosmia as low, medium, or high. Landis et al also followed this questionnaire with a further round of questions aimed at elucidating the impact of parosmia, and those patients with more severe parosmia had greater disruption to their function in eating behaviours and socialising, and were more likely to report weight loss.

Psychophysical testing has proven to be more sensitive in detecting olfactory loss than subjective assessments, and measures the ability to detect validated odorant stimuli and to discriminate between different odours or thresholds for detection of certain odours. Several tests are commercially available, such as Sniffin' Sticks, the University of Pennsylvania smell identification test, and the 12 item, brief smell identification test.[23–25]

While radiological examination has a fairly minor role in the clinical evaluation of most patients with parosmia, some exploratory work using functional MRI (magnetic resonance imaging) scanning[26] has compared the activation patterns in the brains of patients with hyposmia and parosmia when presented with odours. While only a small group was examined, there were findings of interest in differential patterns of activation that might reflect the clinical symptoms shown by each group. Patients with hyposmia demonstrated seemingly typical olfactory stimulation patterns in the parahippocampal gyrus, insula, anterior cingulate cortex, and orbitofrontal cortex, which would be considered to show a so-called normal processing of olfactory stimuli, although reduced from the baseline of patients without hyposmia. By contrast, patients with parosmia showed stronger activation in the putamen—a structure that seems to be critical in recognition of signals of disgust—and the thalamus, which is thought to be responsible for regulating the direction of attention towards a stimulus. This functional MRI study therefore seems to offer objective correlation with the clinical symptoms reported by individuals with parosmia—that is, that they perceive odours as unpleasant and almost overpowering their ability to continue to function where others might perceive a pleasant odour but without it diverting attention from their daily tasks. Such studies are welcome in their addition to better understanding the consequences of olfactory dysfunction; the next section will further examine the underlying causes.

Molecular mechanisms in non-SARS-CoV-2 post-viral olfactory dysfunction

Although post-viral anosmia has been recognised for many decades,[3] investigative literature published before the covid-19 pandemic is scarce and based largely on small clinical series and experimental animal models.

Transient loss of smell secondary to viral infections is often ascribed to the associated rhinitis causing inflammation and oedema of the nasal mucosa, resulting in physical impediment of odorant transit to the olfactory receptors. However, where post-viral olfactory dysfunction persists even after the acute nasal congestion, injury to the olfactory neuroepithelium or central processing pathways has been hypothesised to occur.[4 27]

Initial investigations conducted in people with post-viral olfactory dysfunction consistently observed morphological and structural changes in the olfactory neuroepithelium. Particularly, ultrastructural findings revealed both a substantial reduction in the

number of olfactory sensory neurons and microvillar cells, and also disorganisation of the epithelial architecture with olfactory sensory neurons possessing dendrites that did not reach the surface of the epithelium or that were devoid of sensory cilia.[28 29] In an immunohistochemical study of 10 patients with olfactory dysfunction, neuron specific enolase immunoreactivity of the olfactory neuroepithelium was present in the early stage after common cold while completely absent in the late stage.[30] Extensive scarring of the subepithelial tissue[31] and pathological junctions between olfactory and respiratory epithelium have been identified, suggesting that respiratory metaplasia of the olfactory neuroepithelium might occur as a result of infection.[28] However, no clear correlation exists between the severity of the ultrastructural and histological changes and the clinically detectable grade of olfactory dysfunction.[28 32]

Reduction in the volume of olfactory neurons has been replicated in animal models where recombinant neurovirulent influenza A virus induced rapid tissue destruction of olfactory neuroepithelium and apoptosis of olfactory sensory neurons in mice.[33] The induction of apoptosis was considered a strategy to prevent dissemination of neurovirulent viruses into the brain. However, a reduction in number of neurons alone does not fully correlate with clinical symptoms of olfactory loss, so further studies have sought to ascertain the effect of viral infection on the function of the remaining neurons. The effect of intranasal inoculation of Sendai virus (a murine counterpart of human parainfluenza virus, of which type 3 is the major suspected causative agent of post-viral olfactory dysfunction in humans[34]) was shown to impair the sense of smell. This impairment was caused by the virus weakening the ability of olfactory sensory neurons to take up calcium ions after stimulation by suppressing apoptosis of olfactory sensory neurons, thus impairing the normal regenerative ability of the olfactory epithelium. In this in vitro and in vivo model, Sendai virus was shown to persist in both olfactory neuroepithelium and bulb causing olfactory dysfunction but without easily detectable cytopathology.[35]

Viral pathogens have evolved different strategies to invade the central nervous system, including the olfactory route. The detection of viral antigens, including influenza A virus, parainfluenza virus, and adenoviruses, within the olfactory mucosa and the olfactory bulb provided evidence for a potential route of virus entry into the central nervous system.[36] Furthermore, damage to central olfactory pathways after intranasal inoculation of different viruses has been demonstrated in several animal studies.[37 38] It is therefore not surprising for the olfactory neuroepithelium to have viral recognition systems. Animal models have shown that olfactory neuroepithelium and bulb can both mount an antiviral inflammatory response.[36 39 40] Experiments conducted in zebrafish have shown that the interaction between receptors expressed by olfactory sensory neurons and fish rhabdoviruses glycoproteins led to a ultrarapid immune responses and the recruitment of non-conventional CD8 T cells to the olfactory mucosa from the olfactory bulb.[39] By intranasal use of polyinosinic-polycytidylic acid, a synthetic analogue of viral double stranded RNA (which has been established as an immune model of viral infection), investigators observed that damage to the mouse olfactory neuroepithelium was attributed to the cytotoxic effect of elastase released by neutrophils that infiltrate the olfactory mucosa after an innate immune reaction depending on activation of toll-like receptor 3.[40] This receptor is mainly expressed in the apical part of the supporting cells and in the cytoplasm of the acinar cells of Bowman's glands. The olfactory ensheathing cells, Schwann cell-like glial cells, which supported olfactory sensory neurons axons from the olfactory neuroepithelium to the olfactory bulb, were identified as the source of innate cytokines and hypothesised to provide defence against neurotropic micro-organisms.[36]

All these findings underly the importance of the olfactory neuroepithelium and bulb in surveillance and response to potential neuroinvasive viruses. However, the evidence suggests that this immune competence is counterbalanced by immune mediated inflammatory injury to the olfactory neuroepithelium and olfactory bulb. Figure 1 illustrates the putative mechanisms for viral infection induced hyposmia and anosmia.

Molecular mechanisms of SARS-CoV-2 induced olfactory dysfunction

Olfactory dysfunction was found to be a highly prevalent symptom of SARS-CoV-2 infection[41–43] during the early stages of the pandemic, although incidence has waned with more recent SARS-CoV-2 variants.[17] Olfactory dysfunction is also one of the most predominant symptoms in long covid[44–46]; parosmia in particular has shown a tendency towards a drawn out natural history, with several studies confirming that a large number of patients will continue to have the condition more than six months after index SARS-CoV-2 infection.

People infected with the early SARS-CoV-2 variants had a rapid onset and severity of anosmia with relatively little nasal congestion,[15 44] which would argue against a conductive pathogenesis. MRI studies highlighted a selective inflammatory oedema of the olfactory cleft in the absence of obstacle to the air flow in the nasal cavities in a small number of patients, but other series showed that the olfactory cleft remained clear in the majority of patients.[47–49]

Illustration of a relative lack of conductive blockade in SARS-CoV-2 related olfactory dysfunction has turned the spotlight to sensorineural mechanisms. Olfactory sensory neurons within the

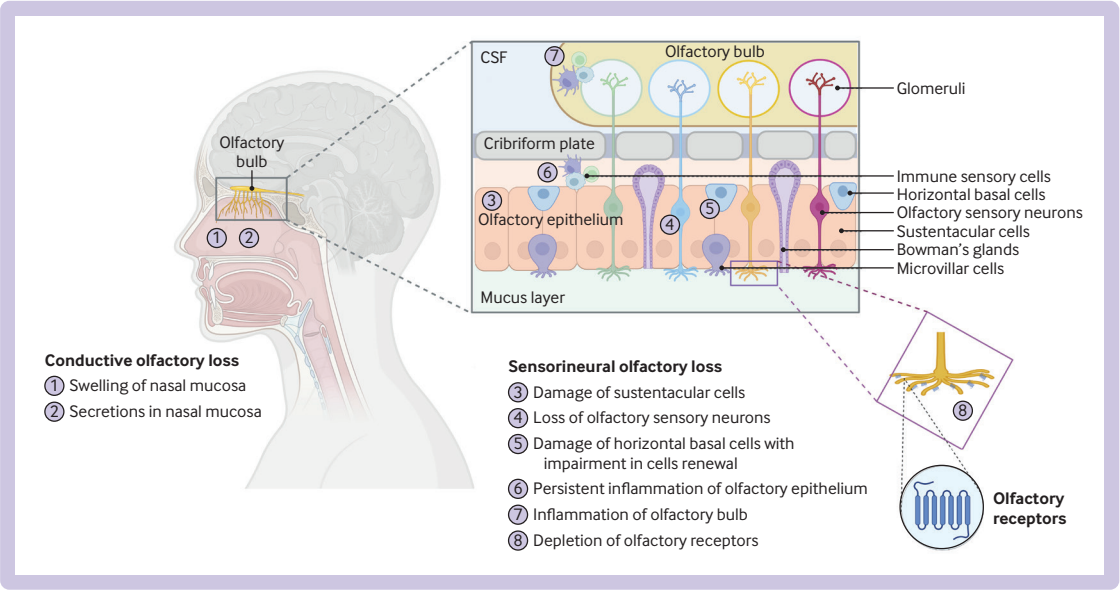

Figure 1 | Putative mechanisms of post-viral olfactory dysfunction. CSF=cerebrospinal fluid

neuroepithelium are bipolar neurons that express the odorant receptors on numerous apical cilia that protrude into the nasal cavity and contain the molecular components for odour transduction.[50] Olfactory sensory neurons are enveloped by sustentacular cells, a type of supporting column shaped cells. At the base of the olfactory epithelium are stem cells that are pluripotent and can replace both sustenacular cells and olfactory sensory neurons, forming a neurogenic niche with regenerative capabilities.[51 52] Studies using single cell, RNA sequencing datasets and immunohistochemistry studies identified that sustentacular and pluripotent stem cells show the molecular makeup that makes these cells prone to SARS-CoV-2 infection—that is, angiotensin converting enzyme (ACE) 2 receptor and transmembrane 2 serine protease (TMPRSS2). Conversely, these markers are not expressed by the olfactory sensory neurons.[53–55] A hamster model of SARS-CoV-2 infection and human postmortem samples of olfactory neuroepithelium have correlated these findings—that sustentacular cells are the main target cells for SARS-CoV-2 infection and replication.[56 57] The small number of infected neurons and lack of evidence of viral replication suggest that olfactory sensory neurons are not the prime direct target of SARS-CoV-2.[58] Rather than direct injury, olfactory sensory neurons could be a downstream victim of sustentacular cell infection because the injured support cell is unable to sustain the olfactory sensory neuron function.

The mechanism that leads to the damage of sustentacular cells after SARS-CoV-2 infection remains unclear. Syncytia formation has been hypothesised as one possible mechanism, based in part on extrapolation of findings of lung tissue in post mortem studies of patients who have died from acute SARS-CoV-2 infection.[59–61] Syncytia formation are thought to contribute to viral replication through facilitating cell-cell spread while evading the extracellular environment and the innate immune system existent within it. SARS-CoV-2 spike protein interacts with the ACE2 receptor to produce virus-cell and cell-cell fusion with this process being amplified by the TMPRSS2 protease.[59] The TMEM16F protein, a calcium-activated scramblase and ion channel[60] has been shown to be involved in the formation of syncytia.[61] ACE2 and TMEM16F were shown to be coexpressed both at RNA and protein levels in sustentacular cells, supporting the hypothesis of pathological syncytia formation.[62]

Acute sustentacular injury might account for early phase olfactory dysfunction, but more widespread changes induced in the olfactory pathway by SARS-CoV-2 could account for longlasting symptoms. After infection, SARS-CoV-2 has been observed to disrupt the nuclear architecture and interfere with olfactory sensory neurons' transcriptome, influencing a persistent downregulation of olfactory receptor proteins and olfactory receptors signalling genes in human olfactory sensory neurons.[58] Alterations in the central nervous system resulting from the inflammatory cascade associated with SARS-CoV-2 infection might also account for longlasting olfactory dysfunction, independent of direct viral induced injury. Initial concerns regarding the neurotropic potential of coronavirus facilitating retrograde spread through the olfactory system and into the central nervous system were refuted by the absence of SARS-CoV-2 RNA in neural and glial bulbar and central compartments.[56 63 64] Furthermore, ultrastructural and molecular alterations were rarely and inconsistently observed in central nervous system olfactory structures in patients with covid-19 who

had died.[56 64–66] In a post mortem assessment of olfactory bulb and tract tissues, axonal degeneration and microvascular endothelial injury were observed in the absence of viral infection, suggesting that these alterations might be the result of immune system activation and inflammation.[66] Sampling of olfactory tissues from patients showing long term persistence of covid-19 associated anosmia revealed the presence of inflammatory transcriptional signature for interleukin (IL) 6, type I interferon, and CXC motif chemokine ligand (CXCL10).[67] In another post mortem study, the olfactory bulb of patients with covid-19 showed a high degree of astrogliosis and microgliosis and a minor infiltration by cytotoxic T lymphocytes.[68] T cell infiltration, partial depletion of olfactory sensory neurones, and the absence of detectable SARS-CoV-2 RNA have also been seen in biopsies taken from patients with objectively proven persistent olfactory loss after covid-19.[69]

By comparing MRI before and after SARS-CoV-2 infection, brain related abnormalities mainly affecting the limbic and olfactory cortical systems were observed.[70] These alterations were interpreted as the consequence of repeated olfactory sensory deprivation rather than the cause of smell loss, with loss of sensory input leading to a loss of grey matter in these olfactory related brain regions. Similarly, the decreased olfactory bulb volume observed in several studies is likely due to the loss of trophic stimuli from the olfactory neuroepithelium.[71]

Pathophysiology of parosmia

For many years, the most plausible hypothesis for parosmia was thought to be aberrant regeneration of olfactory neurons after the acute viral insult, with so-called miswiring, resulting in resulting in neurons that would normally be associated with foul smells being triggered by inoffensive odour molecules. This theory was described by Doty in 1979[72] and is an attractive hypothesis for several reasons—in particular, the observation that many instances of parosmia occur 45-60 days after viral infection, a timescale that parallels the period required for regeneration of olfactory receptors. This miswiring theory after injury to olfactory neurons has been shown in murine models,[73] where transection of the olfactory nerve has been observed to result in the disruption of the odour map. Loss of the proper axonal organisation leads to incorrect projection of axons to their appropriate glomeruli targets and thus is thought to lead to central mischaracterisation of odours.

Although this theory was held as plausible for several decades, the vast numbers of patients affected by SARS-CoV-2 associated olfactory dysfunction has refocused attention on the subject. Authors such as Parker et al[74] have observed that key characteristics of parosmia are not entirely explained by the miswiring theory—for example, where aberrant axonal regeneration would be expected to be random and irregular, there is a typical battery of odours hat commonly trigger parosmia in individuals (such as coffee, meat, egg, garlic, and onion) that are consistently perceived as faecal and foul. Parker and colleagues attempted to expand on the current understanding of peripheral mechanisms of parosmia by testing the hypothesis that parosmia is due to incomplete characterisation of all the constituent components of an odour. They tested this theory using a group of patients with parosmia, both secondary to SARS-CoV-2 and other viruses, who identified coffee as a newly offensive odour. The study group was exposed to specific molecular components that comprised the coffee odour and asked to identify which component triggered parosmia. This study showed not only an incomplete characterisation of odours, but also a common set of compounds with low odour threshold (ie, they were detectable even at very low concentration) that tended to trigger parosmia in patients. This model of unopposed detection of highly volatile odour compounds without the counterbalance of detection of other, more pleasant, odour profile aspects could account for the regular and non-random range of triggers described by individuals with parosmia.

Investigation of central causes of parosmia have been aided by the development of increasingly sophisticated imaging studies. MRI studies of parosmia in the early 2000s where simple volumetry showed a reduction in olfactory bulb volume in patients with qualitative loss compared with those with pure quantitative loss.[75 76] These studies have evolved to those showing specific loss of grey matter in anatomical regions of patients with parosmia such as the anterior insula, anterior insulate complex, and hippocampus that are critical to odour discrimination and memory,[77] as well as functional studies showing differential activation of central pathways in patients with parosmia on exposure to typically inoffensive odours.[26] MRI has also been combined with fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning to illustrate hypometabolism in insula and hippocampus in a case report of a patient with parosmia.[78] Rapid development of ever more detailed imaging studies will no doubt continue to uncover further subtleties in the central pathways affected by parosmia. But whether these observed central changes reflect the cause or effect of parosmia remains unclear. However, an interplay seems likely between both central pathways and peripheral mechanisms of aberrant odour presentation that result in development of parosmia and its persistence in some individuals. Figure 2 illustrates theories of the pathophysiology of parosmia.

Outcomes after post-viral olfactory dysfunction

The prognosis for patients with long term olfactory dysfunction is uncertain, with scope for spontaneous recovery at least three years from onset.[79 80] Lee et al[80]

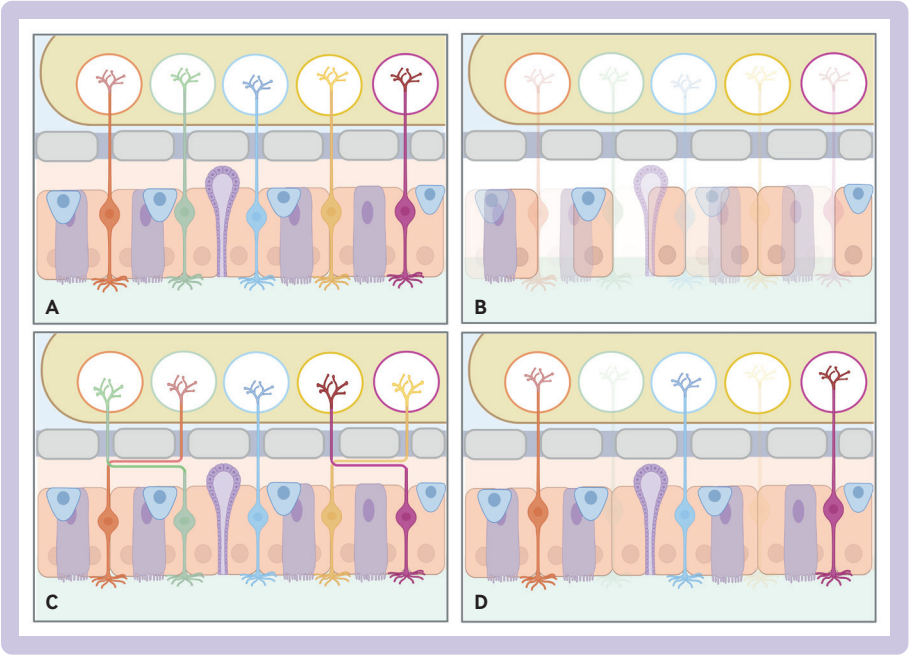

Figure 2 | Potential mechanisms of parosmia. (A) Normal arrangement of olfactory neuroepithelium and its central projections; this image shows the bipolar olfactory sensory neurons, supported by sustenacular cells, and basal cells. (B) Viral induced disruption of the neuroepithelium, with loss of olfactory sensory neurons, sustenacular cells, and basal cells. (C) In the so-called miswiring hypothesis of parosmia, aberrant neural regeneration leads to formation of random and incorrect axonal connection. (D) In the hypothesis of incomplete neural regeneration of parosmia, whereby correct axonal regeneration occurs but only for selected receptor types, leading to incomplete characterisation and misclassification of an odour owing to failure to detect all odour molecular components

prospectively evaluated 63 patients with post-viral olfactory loss using telephone interviews. Patients were asked to subjectively evaluate their olfactory performance on a 100 point scale, and followed for a mean duration of 33.4 months. The researchers saw subjective improvement in olfactory dysfunction in 85.7% of patients, and a return to normosmia in 31.7% of patients. In a retrospective analysis of 791 patients with post-viral olfactory dysfunction evaluated using Sniffin' Sticks testing, Cavazzana et al[81] reported that 46% of patients who initially had anosmia showed clinically significant improvement in olfactory function, as did 35% of patients who initially had hyposmia. Mean follow-up for these patients was 23 months. Overall, a steady rate of recovery is noted up until around one year, after which the rate of recovery slows steadily. After covid-19, the reported prevalence of olfactory dysfunction was 27-60% at six months,[44 82 83] 26.5-46% at one year,[83 84] and 8.3% at two years.[20]

Mechanisms that underpin a prolonged recovery course are not fully understood, but some predictive factors have been associated with a higher recovery rate[85]: patients without coexisting nasal congestion; younger age,[79 80] non-smokers,[86] higher number of receptor cells and intact nerve bundles at the olfactory epithelium biopsy,[32] presence of olfactory event-related potentials,[87] and a narrow width of olfactory bulb when measured radiographically[88]; and lower severity and duration[80 86 89] of olfactory dysfunction at the first visit. Female individuals have notably lower rates of recovery, although the reasons for this are not clear and might be influenced by baseline olfactory function and the influence of oestrogen on the ACE2 receptor.[85]

Outcomes after parosmia

Recovery from parosmia runs a variable course. Some evidence indicates that presence of parosmia after a viral infection could be associated with increased likelihood of eventual olfactory recovery[86 90] compared with those individuals with pure quantitative loss, but other studies have failed to replicate these findings.[90] This heterogeneity might in part be due to baseline regenerative capacity, which declines with age[91]; cause of olfactory dysfunction; and duration and method of follow-up. It also reflects some fundamental research questions in the specialty—namely, how to objectively measure parosmia and how to define recovery as anything other than a binary presence or absence. Most studies have used measures of recovery using quantitative testing and have defined recovery of olfactory function in these quantitative terms, with difficulty in exploring the recovery of parosmia as a symptom.

The vast number of patients affected by SARS-CoV-2 olfactory dysfunction has allowed large scale studies to help resolve some of these questions of recovery in this specific cohort. A prospective multicentric study studied 147 patients with olfactory

dysfunction after self-reported upper respiratory tract infection, and were separated into those with confirmed SARS-CoV-2 on polymerase chain reaction (PCR) testing, and those without. Patients underwent testing with Sniffin' Sticks at presentation and at first follow-up visit, at a mean of 3.4 months follow-up. In addition, patients were asked questions regarding the intensity, frequency, and functional consequences of parosmia. This study showed that patients with parosmia, and particularly younger patients with parosmia, were more likely to recover olfactory function than those without parosmia.[92] Patients with and without SARS-CoV-2 showed a similar improvement over the two visits, although patients with SARS-CoV-2 had a higher baseline of olfactory function.

There is reason for cautious optimism for most patients, because although recovery might be slow after initial SARS-CoV-2 infection (with large numbers still with parosmia at six months),[44] about 85% of patients will no longer report qualitative olfactory dysfunction after two years.[93]

Management of post-viral olfactory dysfunction

Non-drug treatments

Table 2 gives a summary of the evidence regarding non-drug treatments for post-viral olfactory dysfunction.

Counselling

Persistent olfactory disorders and their effects on patients' quality of life might be underestimated by both general practitioners and otolaryngologists.[94] Ninety five per cent of patients report that they have not been able to obtain any counselling before

Table 2 | Non-drug treatment options for post-viral olfactory dysfunction

Author	Year	Study design	No of participants	Intervention	Measures	Outcomes	Numerical results
Pires et al[99]	2022	Randomised, controlled	80	Classical olfactory training, four odours; advanced olfactory training, eight odours; olfactory training for 4 weeks	University of Pennsylvania Smell Identification test, visual analogue scale	Score improvement in University of Pennsylvania Smell Identification test	Post-intervention improvement: advanced olfactory training=1 (range -7 to 10, interquartile range 4); classical olfactory training=1.7 (-7 to 12, 5); P=0.28
Vandersteen et al[100]	2022	Prospective cohort	43	Olfactory training for 6 months	Sniffin' Sticks test; SF-36 questionnaire	Sniffin' Sticks test threshold discrimination identification improvement	Pre-intervention mean score 24.7 (standard deviation 8.9), post-intervention mean score 30.9 (9.8); P<0.001
Choi et al[101]	2021	Non-randomised, controlled	104	Olfactory training for 3 months *v* no olfactory training	Sniffin' Sticks test; visual analogue scale	Identification improvement in Sniffin' Sticks test threshold discrimination	Pre-intervention scores: olfactory training 17.5 (standard deviation 6.1) *v* no olfactory training 15.6 (6.5), P=0.14; post-intervention scores: olfactory training 22.1 (6.8) *v* no olfactory training 18.3 (5.6), P=0.003
Altundag et al[102]	2015	Non-randomised, controlled	85	Classical olfactory training with four odours; modified olfactory training with 12 odours; no olfactory training; intervention performed for 36 weeks	Sniffin' Sticks test, visual analogue scale	Identification improvement in Sniffin' Sticks test threshold discrimination	Pre-intervention mean scores: classical olfactory training 18.1; modified olfactory training 18.2; no olfactory training 18; $F(^{76})<1.82$; P>0.16. Post-intervention mean scores: classical olfactory training 26.3; modified olfactory training 24.3; no olfactory training 19.7; $F(^{246})>11.9$, P<0.001
Damm et al[103]	2014	Randomised, single blind, controlled, crossover	144	High odorant concentration olfactory training *v* low concentration olfactory training for 16 weeks; groups crossed over after 16 week period	Sniffin' Sticks test, visual analogue scale	Percentage of patients with improvement in Sniffin' Sticks test threshold discrimination identification	High concentration olfactory training improvement 25.7%; low concentration olfactory training 14.9% (P=0.11) at 16 weeks; crossover period: improvement in low to high olfactory training 30.8%; high to low olfactory training 45.8% (P=0.07)
Liu et al[114]	2021	Retrospective cohort	153	Olfactory training with subgroup analysis of patients with parosmia	Sniffin' Sticks test	Clinically relevant recovery of overall olfactory function (defined as improvement in threshold discrimination identification of ≥5.5 points)	Odds ratio for olfactory improvement 1.12 (95% confidence interval 0.59 to 2.46), P=0.62; threshold 1.11 (0.53 to 2.33), P=0.78, discrimination 2.88 (1.25 to 6.11), P=0.006, identification 3.38 (1.50 to 7.60), P=0.003

SF-36=36 item short form survey.

referral to a tertiary centre with special interest in the treatment of smell disorders.[95]

Olfactory dysfunction is associated with depression,[96] and patients with more severe quantitative loss have more severe depression scores as measured by validated questionnaires such as the Beck depression inventory. Patients with parosmia and quantitative olfactory dysfunction show greater disruption to their daily life than patients with quantitative olfactory impairment alone; there are barriers to activities such as cooking, eating, and social interaction owing to an association with foul smell perception.[97] Their overall quality of life is worse than those individuals with pure quantitative loss.

Olfactory training

First proposed by Hummel et al in a non-randomised controlled trial of 56 patients in 2009,[98] evidence suggests that olfactory training might be useful in the treatment of both quantitative and qualitative post-viral olfactory disorders.[99–103] The mechanisms underlying its effectiveness are not fully understood but has been hypothesised to either harness the regenerative capacity of neurons at the level of the olfactory epithelium through exposure to repeated olfactory stimuli[104 105]; or more plausibly to have a top-down effect is also possible because olfactory training also induces cortical thickening in the olfactory area of the brain,[105] strengthening of olfactory, somatosensory and integrative networks,[106] and volumetric increase in the olfactory bulb.[107] The second hypothesis is also supported by the meta-analysis by Sorokowska et al,[108] which analysed 11 studies totalling 879 patients. The investigators found that olfactory training has a significantly positive effect on olfactory ability as measured by the Sniffin' Sticks test (Hedges g 1.10, 95% confidence interval 0.459 to 1.734). The effects are greatest in the ability to discriminate (0.89, 0.498 to 1.298) and identify (0.833, 0.264 to 1.402); and small to moderate in lowering the olfactory threshold for detection of odours (0.336, 0.103 to 0.569).

In the classic olfactory training protocol, patients use four odorants and consciously spend 10 seconds smelling each, twice a day, for three months.[98] Over time, modifications of this protocol have been proposed, extending the duration up to eight months,[102 103 109] periodically changing the odorants[102] or increasing their concentration[103] with potential benefits on the effectiveness of the treatment.

To date, olfactory training is the one treatment with effectiveness most solidly demonstrated for post-viral olfactory dysfunctions. For this reason, and because of the absence of side effects and the ease of access, olfactory training is recommended by expert consensus as the first line treatment for post-viral olfactory loss.[110–113]

The application of olfactory training in parosmia has also been tested in a study of 153 patients with post-infection olfactory dysfunction,[114] which showed that those with parosmia were more likely to benefit from meaningful improvement in their ability to identify and discriminate odours than patients with quantitative loss only. The authors of this study hypothesised that this finding could be related to central mechanisms of parosmia where incomplete or incorrect presentation of odour stimuli can be reordered through the top-down influence of olfactory training.

Drug treatments

Table 3 presents a summary of the evidence surrounding drug treatments in post-viral olfactory dysfunction.

Corticosteroids

The use of both oral and topical corticosteroids in post-viral olfactory dysfunction has been investigated, although not with specific reference to parosmia. With the caveat of limited evidence, support is expressed for topical steroids delivered as a rinse, with significant improvement shown when used alongside olfactory training compared with use of olfactory training alone.[115] Topical steroid rinses are generally well tolerated, with a relatively benign side effect profile including nasal drying and mild epistaxis. Topical steroid sprays, by contrast, have limited available evidence for evaluation. A double blind, randomised controlled trial has investigated the use of topical steroid sprays in 40 patients who were previously treated with oral steroids; no additional benefit was seen in those receiving topical sprays.[116] For a systematic review of the use of corticosteroids in olfactory dysfunction after SARS-CoV-2 infection, researchers performed an analysis of all forms of intranasal corticosteroid delivery, both in rinse and spray form.[117] They identified five studies for inclusion, totalling 696 patients studied, and found no significant difference (odds ratio 1.43, P=0.08) in the rate of recovery from olfactory dysfunction between the treatment and control groups.

Oral steroid use receives only weak support from the international consensus document, with a recommendation for their use only after discussion regarding the risks and benefits for each individual patient.[111] A randomised controlled trial that allocated 115 patients with post-covid-19 olfactory dysfunction to receive prednisolone or placebo showed no benefit in systemic steroids.[118] Therefore, the use of systemic steroids has to be carefully considered in its risk/benefit profile for each patient with counselling regarding their well known adverse effects.

Table 3 | Drug treatment options for post-viral olfactory dysfunction

Author	Year	Study design	No of participants	Interventions	Measures	Outcomes	Numerical results
Nguyen et al[115]	2018	Randomised controlled trial	138	Olfactory training with saline irrigations or olfactory training with budesonide irrigations	University of Pennsylvania Smell Identification test	Percentage of patients with clinically relevant improvement in University of Pennsylvania Smell Identification test (change in score of ≥5)	Odds ratio 2.1 (95% confidence interval1.03 to 4.41), P=0.039
Blomqvist et al[116]	2003	Double blind, randomised controlled	40	Flutucasone oroprionate *v* placebo *v* control	Butanol odour test	Percentage of patients with at least two step improvement in butanol odour test	No significant difference (P>0.05)
Schepens et al[118]	2022	Double blind, randomised controlled	115	Prednisolone 40 mg once daily for 10 days *v* placebo	Sniffin' Sticks test	Median threshold discrimination identification score	Threshold discrimination identification: placebo median 26.8 (interquartile range 23.6-29.3) *v* intervention median 28.8 (24.0-30.9), P>0.05
Philpott et al[119]	2017	Double blind, randomised controlled	55	Sodium citrate nasal spray *v* placebo	Olfactory thresholds for palmitoylethanolamide over 2 hours	Improvement in palmitoylethanolamide threshold	Control median threshold 0 (interquartile range 0-0.5); intervention median threshold 1 (0-2), P=0.014
Whitcroft et al	2016	Single blind, controlled trial	49	Topical sodium citrate *v* placebo	Sniffin' Sticks test	Change in composite threshold and identification scores	Mean change in score: sodium citrate 0.33 (standard deviation 2.34); placebo −0.54 (2.62); mean difference 0.87 (2.68); P=0.04
Whitcroft et al[120]	2021	Controlled trial	60	Topical sodium citrate *v* placebo	Sniffin' Sticks test	Change in composite threshold discrimination identification score for quantitative loss; percentage of patients reporting qualitative loss	No significant difference in mean change in threshold discrimination identification score; no significant difference in total number of patients reporting qualitative loss
Hummel et al[122]	2017	Retrospective, cohort	170	Topical vitamin A plus olfactory training *v* olfactory training alone	Sniffin' Sticks test	Percentage of patients achieving a clinically significant improvement in threshold discrimination identification score (defined as +5.5 points)	Intervention group 37% *v* control 23% (x^2 7.06, degrees of freedom=2, P=0.03)
Reden et al[123]	2012	Double blind, randomised controlled	52	Oral vitamin A *v* placebo	Sniffin' Sticks test	Mean threshold discrimination identification score	Mean threshold discrimination identification: intervention group 18.34 (standard error of the mean 1.42); placebo group 20.11 (1.43); P=0.47
di Stadio et al[124]	2022	Double blind, randomised controlled	185	Oral PEA-LUT plus olfactory training *v* olfactory training alone	Sniffin' Sticks test	Mean threshold discrimination identification score	Mean threshold discrimination identification: intervention group 29.8 (standard deviation 7.5); control group 19.5 (7.3); P<0.001
Yan et al[127]	2022	Prospective, randomised controlled trial	87	Oral omega 3 supplementation plus nasal rinse *v* nasal rinse alone	University of Pennsylvania Smell Identification test	Percentage of patients with clinically significant olfactory loss (≥10% reduction of University of Pennsylvania Smell Identification test scores *v* patient's own baseline)	Intervention group 4.3% *v* control 24.4% (P=0.01)
Yan et al[125]	2020	Case series	7	Intranasal injection of platelet rich plasma	Sniffin' Sticks test	Mean threshold discrimination identification	Mean threshold discrimination identification: pre-treatment 23.6 *v* post-treatment 19.5, P=0.026
Yan et al[126]	2022	Randomised controlled trial	35	Three intranasal injection of platelet rich plasma plus budesonide rinse *v* three intranasal saline injections plus budesonide rinse	Sniffin' Sticks test	Change in mean threshold discrimination identification versus baseline	Mean change from baseline: intervention group 6.25 points (95% confidence interval 3.85 to 8.65) (P<0.001) *v* control group 1.17 points (−1.99 to 4.32) (P>0.05)
Garcia et al[128]	2022	Case series	12	Gabapentin, up titrated from 100 mg to 600 mg, once daily plus olfactory training and budesonide rinse	Subjective assessment of parosmia	Subjective assessment of severity of parosmia	Improvement in 8 of 12 patients

Calcium buffers

Intranasal sodium citrate is a calcium sequestrant, reducing free mucosal calcium with subsequent inhibition of negative feedback and increasing sensitivity to odours. It has a positive effect on olfaction that lasts minutes to hours, as seen in one randomised controlled trial[119] and one relatively small trial where 49 patients acted as their own control using the contralateral nostril.[120] The authors of this second trial performed a second follow-up study that followed patients using the same protocol over prolonged use of intranasal calcium citrate.[121] Despite no effect noted on quantitative function, a reduction was seen in the proportion of patients reporting phantosmia (though not parosmia). This finding suggests that this treatment might be a promising avenue for investigation of the use of intranasal sodium citrate in olfactory dysfunction, and given its low side effect profile, remains an option for treatment in patients with post-viral olfactory dysfunction.

Vitamin A

Vitamin A has been hypothesised to have favourable effects in neural regeneration, and as such has been studied in both topical/intranasal and systemic use in patients with post-viral olfactory dysfunction. Topical vitamin A seems to be the more promising format, as shown in a retrospective cohort trial (n=124) by Hummel et al.[122] Patients with olfactory dysfunction after infection received both olfactory training and topical vitamin A, and their olfactory outcomes were compared with a cohort of patients receiving olfactory training alone. The addition of vitamin A resulted in significantly better quantitative olfactory function at 12 weeks, although with the noted limitation that no randomisation was performed in this cohort study. The same group of researchers did an earlier trial of systemic vitamin A in 52 patients with both post-infectious and post-traumatic olfactory loss with no evidence of benefit[123]; with no other high quality studies performed to counter this evidence. Therefore, while the evidence for intranasal vitamin A is weakly in favour, there are sufficient grounds for the International Consensus of Allergy and Rhinology authors to make recommendations against systemic vitamin A.

Palmitoylethanolamide and luteolin

Palmitoylethanolamide and luteolin (PEA-LUT) are hypothesised to reduce neuroinflammation by modulating microglia and reducing reactive oxygen species; and as such, have been applied to patients with post-viral olfactory dysfunction. In a double blind, randomised, placebo controlled trial of PEA-LUT, 92% of 130 patients in the intervention group showed an improvement in olfactory function versus 42% of 55 controls at 90 days.[124] Further studies will be needed to understand by what mechanism PEA-LUT influences recovery of olfaction, and to replicate these results to support its efficacy in post-viral olfactory disorders.

Omega 3

Omega 3 are fatty acids that normally make up cell membranes. Omega 3 supplementation has a therapeutic potential via direct neuroprotective effects and increases production of antioxidant and anti-inflammatory amino acids. Its use has been proposed by Yan et al in a randomised controlled study of 87 patients in 2020[125] for the treatment of olfactory dysfunctions resulting from endoscopic approaches to sellar and parasellar tumours. At three and six months, patients treated with the omega 3 supplement showed a significantly lower rate of persistent olfactory dysfunction than controls. Given the relatively minor and infrequent side effects, supplementation with omega 3 is a therapeutic option that can be taken into consideration, despite the need for larger studies to establish its effectiveness in post-viral olfactory dysfunctions.

Platelet rich plasma

Platelet rich plasma is an autologous biological product derived from the patient's blood, and is rich in platelets and pro-regenerative factors. In a pilot study by Yan et al,[48 126] platelet rich plasma was inoculated into the olfactory clefts of seven patients with severe post-viral olfactory disorders. These results were then consolidated with a follow-up study from the same group.[127] The follow-up study randomised patients to either a course of three injections of plasma rich plasma to the olfactory epithelium delivered over a four week interval, or saline injections over the same interval. The results indicated that injection with platelet rich plasma resulted in a significantly improved olfaction score at three months as measured by threshold and discrimination scores of Sniffin' Sticks. However, no difference was seen in the patients' subjective assessment of their olfactory function. The authors also found no change in the proportion of patients reporting parosmia after platelet rich plasma. This well designed study illustrates the complex nature of olfactory dysfunction research, in that there is an imperfect correlation between objective improvement on observed measures but without meaningful impact on the patient. Nonetheless, the hypothesis tested in this study—that platelet rich plasma might have a positive influence on peripheral regeneration of olfactory epithelium—is promising and a potential avenue for further investigation.

Gabapentin

Although not tested in a randomised or controlled trial, the use of gabapentin in a small case series of nine patients is worthy of mention because it specifically examined its use in patients with parosmia.[128]

In this case series, 12 patients with parosmia consented to an empirical trial of gabapentin, with titration from 100 mg daily to a maximum of 600 mg daily. This treatment was combined with topical steroid rinse and a form of olfactory training. Two patients were unable to tolerate gabapentin's side effects, while one patient stopped taking it before the defined endpoint of three weeks of maximal tolerated dose. Of the nine patients who were able to tolerate the maximum dose of gabapentin for three weeks, eight reported clinically significant improvements in their symptom of parosmia. At follow-up, two patients who attempted to wean from gabapentin reported worsening of symptoms while one was able to stop without recurrence. Although this series of observed outcomes is very small, it holds interest for the use of neuromodulators in the treatment of parosmia. The relatively high dropout rate speaks to the difficulty that many patients will have in tolerating this treatment, and as such, it should be the subject of further robust investigation before an unequivocal recommendation for use.

Emerging treatments

Traditionally, treatments aimed at postviral olfactory dysfunction have often aimed at the presumptive inflammatory or conductive component, with corticosteroids delivered either topically or systemically. However, the emerging understanding of the central pathways of post-viral olfactory dysfunction and parosmia in particular have seen attention turn towards neuromodulators and agents that can positively influence neural regeneration. As described above, some promising evidence supports agents such as topical vitamin A, PEA/LUT, and platelet rich plasma injections to the olfactory mucosa. Gabapentin has only the very earliest suggestion of efficacy, but represents a notable angle on systemic neuromodulation. When combined with the top-down reordering of olfactory pathways as influenced by olfactory training, it seems certain that future developments in the treatment of olfactory disorders will address the peripheral and central neural pathways rather than inflammation at a purely mucosal level.

QUESTIONS FOR FURTHER RESEARCH

- ⇒ What percentage of patients with olfactory dysfunction currently classified as idiopathic could have an identifiable cause if biomarkers of disease were present?
- ⇒ What are the patient and disease predictors of olfactory recovery after viral infection?
- ⇒ Could early use of interventions such as olfactory training in post-viral olfactory dysfunction prevent the development of parosmia?

PATIENT INVOLVEMENT

The content of this article was reviewed by a fellow healthcare worker who had post-viral olfactory dysfunction and parosmia after contracting SARS-CoV-2 in the first wave of the pandemic in 2020. In addition, the present review references work from the UK charities AbScent and Fifth Sense, who have been heavily involved in high quality, patient centred, olfactory research.

Guidelines

At present, limited therapeutic options are available for patients with post-viral olfactory disorders. There is a lack of randomised trials with appropriate controlled arms and reliable olfactory assessment. This paucity was mentioned in the 2022 guideline, the International Consensus Statement in Allergy and Rhinology: Olfaction.[111] This guideline was the result of a wide ranging review that comprehensively looked at published evidence in olfactory therapeutics but with only one (olfactory training) reaching an outcome of unequivocal recommendation.[111] The quality of evidence was noted to be particularly low in the specific question of parosmia. This consensus document, although exhaustive in its review of published data, is limited in its ability to rapidly respond to evolving evidence that emerges after its publication. Living reviews such as the Cochrane Review of post-SARS-CoV-2 olfactory dysfunction have attempted to resolve this limitation,[112] by continually being updated according to the availability of data. Again, the evidence at this review was noted to be sparse when considering published randomised controlled trials. Case reports and cohort studies abound, but are limited in their interpretation owing to the natural history for parosmia to improve over time regardless of intervention. As such, this review will also limit its consideration to interventions with a specified control group, or systematic reviews and meta-analyses of the topic.

Conclusions

The high prevalence of olfactory dysfunction after infection with SARS-CoV-2 has provided an unseen opportunity to study the underlying pathophysiological mechanism of post-viral olfactory loss, with considerable advances in the field, which could yield novel therapeutic options. However, the underlying mechanism and treatments for qualitative olfactory disordersr remain elusive, yet the large burden of disease following the pandemic makes this an important focus of future research.

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