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REVIEW ARTICLE

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Recovery rates and long-term olfactory dysfunction following COVID-19 infection

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Abstract

Objectives: Olfactory dysfunction is one of the most recognized symptoms of COVID-19, significantly impacting quality of life, particularly in cases where recovery is prolonged. This review aims to explore patterns of olfactory recovery post-COVID-19 infection, with particular focus on delayed recovery.

Data Sources: Published literature in the English language, including senior author's own work, online and social media platforms, and patients' anecdotal reports.

Method: A comprehensive review of the literature was undertaken by the authors with guidance from the senior author with expertise in the field of olfaction.

Results: Based on self-report, an estimated 95% of patients recover their olfactory function within 6 months post-COVID-19 infection. However, psychophysical testing detects higher rates of persistent olfactory dysfunction. Recovery has been found to continue for at least 2 years postinfection; negative prognostic indicators include severe olfactory loss in the acute phase, female sex, and older age. Variability in quantitative and qualitative disturbance in prolonged cases likely reflects both peripheral and central pathophysiological mechanisms. Limitations of many of the reviewed studies reflect lack of psychophysical testing and baseline olfactory assessment.

Conclusions: Post-COVID-19 olfactory dysfunction remains a significant health and psychosocial burden. Emerging evidence is improving awareness and knowledge among clinicians to better support patients through their olfactory rehabilitation, with hope of recovery after several months or years. Further research is needed to better understand the underlying pathogenesis of delayed recovery, identify at risk individuals earlier in the disease course, and develop therapeutic targets.

KEYWORDS

anosmia, COVID-19, olfaction, parosmia, recovery

Key points

- It has been widely reported that smell/taste dysfunction resolves substantially by 2 weeks of COVID-19 infection. However, millions suffer with continued

chemosensory dysfunction, years after initial infection and there is evidence that recovery continues for several years post-COVID-19 infection.

- When assessing literature regarding recovery rates, one must be mindful of the lack of baseline olfactory assessment before infection, and whether recovery was evaluated using self-reported questionnaires or psychophysical testing.
- Olfactory training should be considered when discussing treatment options with patients with long-term olfactory dysfunction following COVID-19.
- This review aids in further understanding, risk factors, pathophysiology, and disease trajectory in those affected with long-term chemosensory dysfunction post-COVID-19 infection.

INTRODUCTION

Dysfunction of smell and taste has come to be one of the most well-known symptoms of SARS-COV-2 infection.[1] Globally, an average of nearly 50% of infected individuals reported olfactory and/or taste dysfunction at the onset of the COVID-19 pandemic, often as the initial symptom experienced after COVID inoculation.[1–3] Some of the first published studies on recovery of smell and taste function suggested that the function of most patients returned to normal by 5–7 days.[4] However, despite these early and encouraging reports, it has become clear that a sizeable number suffer with persistent olfactory dysfunction (OD) for several months or even years, living with associated symptoms often detrimental to their quality of life.

Clinicians now acknowledge disturbances to olfaction and gustation as a manifestation of the wide-ranging phenotypes that are commonly referred to as "long Covid."[2] As of March 2023, it was estimated that 1.9 million people in the United Kingdom were experiencing symptoms of long COVID.[5] Despite the fact that the COVID-19 pandemic reinvigorated research into postviral chemosensory disturbance, the underlying pathophysiological processes that influence recovery rates remain to be explained. Although, at the time of the writing of this review, 3 years have passed since the pandemic began, efforts to find therapeutic solutions for such individuals have largely failed.[6]

Awareness of long-term smell dysfunction significantly impacts the lives of those who have been inflicted. As an example, which generalizes to many such individuals, is one patient's report that she is "really struggling, and it's so hard when no one around you understands; the thought of it going on this bad for months on end is unimaginable."[7] Dysfunction in taste and smell affects many daily activities, from personal safety to personal hygiene[8]; several studies have also demonstrated the significant impact on quality of life.[3,7–9] The loss of smell and taste hampers the enjoyment of food and drinks, which for some can be debilitating, as activities that were once a source of enjoyment become a chore, leading to depression, anxiety,[10] and even malnutrition.[7] For many patients, the prolonged and uncertain nature of OD causes a huge burden on their mental health, with some reporting suicidal thoughts.[11] The detrimental impact of smell and taste dysfunction is further compounded by lack of knowledge of the long-term prognosis, which can also lead patients to report not feeling supported by healthcare practitioners.[8,11] A number of these patients have found support on internet groups of similarly affected people, and here they share their frustration with the lack of knowledge regarding recovery rates, or often misinformation, suggesting that by certain time points, there is little hope of recovery.

To address this, we evaluated the current evidence regarding long-term chemosensory dysfunction (CD), following COVID-19 infection to gain a better understanding of prognostic indicators for symptomatic improvement. A review of the literature was undertaken from September 2020 (to capture more persistent loss) until March 2023, using the terms COVID and (olfactory or anosmia or smell) and (recovery or persistence). This generated 10,662 references and therefore a formal systematic review was not undertaken but titles screened for relevant articles.

ASSESSMENT OF RECOVERY

There is large variability in reported rates of recovery.[12,13] This is in part due to the nature of COVID-19 and the challenges of assessing patients at early stages of infection, but also reflects the heterogeneity in outcomes used to both self-report and more formally assess the severity of OD.

Though more difficult to analyse, self-reported outcomes are likely the closest understanding clinicians will have to the patient's own experience of OD, and benefit from not requiring face-to-face contact with infected individuals. Visual analog scales, Likert scales, and questionnaires are used to survey self-reported outcomes.[14] Psychophysical testing of CD allows investigators to quantify the severity of dysfunction. A popular method of evaluating OD is the Sniffin Sticks Threshold, Discrimination, and Identification (TDI) score.[14,15] Normosmia is indicated with a TDI score >30.75, hyposmia TDI 16.25–30.50, and anosmia TDI <16.0.[14] The reusable nature of the Sniffin Sticks, and the need for a researcher to deliver the test face to face prohibited widespread use during the acute phase of the

pandemic. The University of Pennsylvania Smell Identification Test (UPSIT®) is another validated and widely used tool which has the advantage of being single-use and can be self-delivered, without the need for a researcher to be present. Retronasal olfactory function can be tested using powdered tasteless aromas placed on the tongue. Gustatory psychosocial evaluation can be conducted using taste strips containing sweet, sour, salty, and bitter tastes. Several taste tests using such strips are available. In one test, a Taste Stripe Score (TSS) can be used to identify normogeusia TSS >9 points or Hypogeusia TSS <9 points.[14] In another test, which can be self-administered and requires no liquids, percentile ranks are available to identify persons with differing degrees of taste dysfunction.[16]

It has been shown that, in general, patients underestimate the initial prevalence of OD[17,18] and overestimate their recovery on self-reported questionnaires, when compared to psychophysical testing.[19–21] Gözen et al.[18] found objective OD (using TDI scores) in 83% of patients post-COVID-19, where the self-reported loss of taste was 52.5%. The SARS-Cov-2 human challenge study offered a unique opportunity to evaluate olfactory dysfunction in real-time before, during, and after acute infection, with repeated assessment with UPSIT scores.[22] Olfactory function was normal in all patients at baseline, but 83% self-reported smell impairment after inoculation.[22] The duration of OD was short lived in the majority of cases, but interestingly, a small number of patients failed to self-report any loss of sense of smell despite a significant fall in the UPSIT® score, while several reported complete recovery while still demonstrating mild to moderate hyposmia on UPSIT® testing.[22] Prajapati et al.[23] compared self-rating of OD and psychophysical testing with the 12-item Brief Smell Identification Test (B-SIT®) over time and found a moderate correlation between the two scores. Interestingly this study found that patients self-ratings suggested a higher degree of persistent dysfunction than the isolated identification testing revealed. Many patients with long-standing OD after report near-normal identification and discrimination scores on testing but have reduced threshold scores[24] and the B-SIT® therefore may have lacked the sensitivity required to detect this.

The lack of strong correlation between psychophysical testing and patients' self-reported severity of loss likely reflects that patients also consider symptom-related disability, the impact on quality of life, and associated qualitative disturbance, in judging the severity of their symptoms. Therefore, an ideal study will include both outcomes when assessing recovery of OD.

The nature of CD seen after COVID-19 is itself variable. CD encompasses symptoms that easily be quantitatively measured (e.g., hyposmia/anosmia or hypogeusia/ageusia) as well as symptoms that are more difficult to objectively assess (e.g., parosmia or parageusia [distorted sensations], cacosmia or cacogeusia [putrid sensations], phantosmia or phantogeusia [smell or taste hallucinations]).[2] Structured questionnaires have been developed to assist with repeated assessment over time.[25]

Early recovery

It has been widely reported that most individuals with COVID-19 CD rapidly recover their smell and taste.[2,12,26] In their systematic review, Santos et al.[12] evaluated 17 articles, with variance regarding the duration of smell and taste dysfunction, ranging from 5 days to 4 weeks. However, most studies found that smell/taste dysfunction began to resolve in 1 week, with a substantial improvement by 2 weeks.[12]

A recently published individual patient data meta-analysis by Tan et al.[2] evaluated 18 studies with a total of 3699 patients assessing self-reported recovery rates at 6 months postinfection, proportion of persistent loss of smell and taste, and prognostic markers in recovery. This study concluded 74.1% of patients' self-report recovery of smell, and 78.8% reported recovery of taste after 30 days, 95.7% reported recovery of smell, and 98.0% recovery of taste at 180 days, with a predicted 5% having persistent CD. However, this figure may be an underestimate of the true number according to sensitivity analyses conducted.

Identifying prognostic factors are important in targeting potential treatments and informing patients of their likelihood of recovery. Tan et al.[2] found that higher initial severity in smell dysfunction post-COVID-19 infection was associated with poorer recovery of smell. Female sex was associated strongly with poorer smell and taste recovery. Interestingly, a pre-COVID meta-analysis demonstrated that women outperform men in most aspects of olfaction.[27] It is possible that a stronger baseline olfactory ability could cause females to be more sensitive to changes in olfaction, resulting their reporting of larger subjective changes. In contrast, they found that medical comorbidities, body mass index, and symptoms such as cough, fatigue, and rhinorrhoea, had little correlation with the recovery of smell and taste post-COVID-19 infection. Recovery of smell was positively associated with dyspnea and steroid administration.[2]

Based on four studies that examined self-reports of smell recovery, 12.8%–30.4% of patients regained partial function and 44.0%–70.0% complete function at follow-up.[21,28–30] Three studies that evaluated taste recovery reported 8.3%–30.0% gained partial recovery, and 50.0%–88.9% full recovery at follow up.[21,28,30] Follow up time varied from 30 days to 6 months.[2]

Many patients involved in currently published studies and meta-analyses are likely to have been infected by the first alpha variants of SARS-Cov-2. Mutations in D614G, which enhances viral entry into host cells, likely accounted for the variation in prevalence of CD seen in the early phases of the pandemic.[31] With the emergence of the more recent variants, the prevalence of smell and taste dysfunction has markedly reduced. One study demonstrated 13%–16% patients with the Omicron variant had smell and taste dysfunction, compared with 44% of patients with the delta variant.[32] In another study by Vaira et al.,[33] patients self-reported olfactory loss in 72.4% of cases in the D614G group, in 75.4% of cases in the Alpha group, in 65.6% of cases in the Delta group, and in 18.1% in the Omicron group.

Fewer studies report recovery rates from more recent variants. One recently published study by Boscolo-Boscolo-Rizzo et al.[34] evaluated self-reported recovery rates of smell and taste 6 months post-Omicron BA.1 subvariant. Of the 294 patients, 34.4% reported dysfunction in smell or taste during the acute phase of infection, 96% reported complete resolution of their symptoms at 6 months, 2% had

a decrease in severity, and 2% reported worsening of symptoms. Though there were no sociodemographic characteristics associated with the onset of CD, the duration of dysfunction was shorter at 6 days in vaccinated patients, compared to 8 days ($p = 0.007$) in patients with incomplete or no vaccination.[34] A shorter duration of smell and taste dysfunction was also associated with younger age.[34]

Vaira et al.[35] further investigated recovery rates 6 months post-COVID-19 infection when the Omicron variant was predominant. After psychophysical testing of 102 patients with recent COVID-19 infection, 34 patients (33.3%) had olfactory dysfunction at the beginning of the study; this included 16 (15.7%) with anosmia and 18 (17.6%) with hyposmia.[35] At the end of the 6-month follow up period, 80 patients underwent psychophysical testing, where 11.3% were found to have continuing olfactory dysfunction, including eight patients (10%) with hyposmia and one (1.3%) with anosmia.[35] Interestingly, only four patients (5%) self-reported hyposmia at 6 months follow up.

Delayed recovery (>6 months)

Late post-COVID-19 infection recovery rates remain inconsistent in the literature,[12,13] which could be due to differences in methods of reporting, follow-up duration, attrition rates, and inclusion of different variants.[2] However, all longer-term studies are consistent in demonstrating ongoing recovery for several years after onset of post-COVID CD.

A prospective cohort study of 168 patients with mild COVID found that 64% patients reporting COVID-related OD at baseline, compared with 16% at 6 months and 8% at 2 years. Eighty-eight percent of patients self-reported complete recovery of olfactory and gustatory dysfunction, 10.9% occurring after 6 months.[9] A different cohort study from Italy showed a similar rate of late recovery.[36]

A matched case-control study with 2 years follow-up found 71% of patients self-reported complete resolution of CD[14] and 13% reported a decrease in severity of dysfunction in the period from 12 to 24 months postinfection.[14] In the same study, using psychophysical evaluation with the extended Sniffin Sticks test, 42% of patients were shown to have persistent olfactory dysfunction at 12 months, reducing to 28% at 24 months (compared with 11% of controls). A total of 3% patients remained anosmic at 2 years. A different group, using only the identification component, found lower rates of OD, in 24.2% at 6 months, 17.9% at 12 months, 5.8% at 18 months, and 2.9% at 24 months.[15] The lower prevalence likely reflects better recovery in identification scores compared to threshold scores. This study found an association between compliance with olfactory training (OT) protocols and recovery.

There are many anecdotal reports of ongoing recovery from 2 to 3 years postinfection and beyond on social media groups and isolated reports in the literature.[37] Prospective studies reporting 3-year data and beyond are eagerly awaiting but it is clear that hope for recovery remains for those with persistent olfactory dysfunction and it is too early to declare it permanent at the current time.

RECOVERY FROM QUALITATIVE OLFACTORY DYSFUNCTION

The development of parosmia following a COVID-19 infection has been well described in the literature, often with delayed onset weeks or months after initial infection.[38] One study found 8% of patients reported qualitative dysfunction 2 years postinfection, with parosmia and phantosmia being the most common.[36]

Schambeck et al.[39] found a mixture of quantitative and qualitative dysfunction in their prospective study with a mean follow up period of 721 days. At a mean follow-up of 100 days, 23% reported qualitative dysfunction, increasing to 30% at 244 days before reducing to 1% at 721 days. This study also suggested that patients developing qualitative CD following SARS-Cov-2 infection were more likely to report long-lasting olfactory dysfunction. In contrast, a prospective multicentric study studied 147 patients with olfactory dysfunction after self-reported upper respiratory tract infection, including COVID, and showed that patients with parosmia, and particularly younger patients with parosmia, were more likely to recover olfactory function than those without parosmia.[40]

In contrast, Boscolo-Rizzo et al.[41] found that among patients reporting parosmia or phantosmia at any time, more severe quantitative OD was correlated with longer duration of qualitative OD; the median for qualitative OD duration was 406 days in anosmic, 217 days in hyposmic, and 62 days in normosmic participants ($p = 0.030$).

How do recovery rates relate to the pathophysiology of persistent chemosensory dysfunction in COVID infection?

Transient loss of smell is common in viral infections and has been ascribed to infectious rhinitis causing inflammation and edema of the nasal mucosa resulting in physical impediment of odorant transit to the olfactory receptors. A surprising feature of the olfactory dysfunction associated with SARS-CoV-2 was the absence of self-reported nasal congestion in early stages. Olfactory cleft edema may not produce symptomatic obstruction but does not appear to be universally present; one radiographic study found no opacification of the olfactory clefts in the majority of patients with olfactory disturbance postinfection.[42] In contrast, another study found transient edema in the majority of patients imaged soon after infection.[43] Where postviral OD persists after any acute nasal congestion or edema has resolved, it has been hypothesized that there has been injury to the olfactory neuroepithelium or central processing pathways.[44,45]

It is thought that the SARS-CoV-2 virus initially causes olfactory disturbance by eliminating sustentacular cells expressing ACE-2.[46–48] Studies using single-cell RNA-sequencing data sets and immunohistochemistry studies identified that sustentacular and pluripotent stem cells, but not olfactory receptor neurons (ORNs), exhibit ACE-2 receptor and TMPRSS2 serine protease required for viral entry and

infection in SARS-CoV-2.[32,38,49] A hamster model of SARS-CoV-2 infection and human postmortem samples of olfactory neuroepithelium suggest that sustentacular cells but not ORNs as the main target cells for SARS-CoV-2 infection and replication.[48,50] The small number of infected neurons and the lack of evidence of viral replication suggest that ORNs are not the prime direct target of SARS-CoV-2. Rather than direct injury, ORNs may be a downstream victim of sustentacular cell infection; if rapid recovery of the sustentacular cells occurs, ORNs may survive the initial insult, and functionality is restored, in keeping with the reports of high rates of early recovery. If the sustentacular cells fail to recover rapidly, loss of ORNs may follow. Subsequent recovery is dependent upon repopulation of the ORNs; the regenerative capacity of the olfactory epithelium diminishing with age in keeping with the rates of recovery seen with increasing age.

Sampling of olfactory tissues from patients showing long-term persistence of COVID-19-associated anosmia and animal models of infection showed the presence of inflammatory transcriptional signature for interleukin-6, type I interferon, and other inflammatory cytokines.[48] T-cell infiltration, partial depletion of olfactory sensory neurons, and the absence of detectable SARS-CoV-2 RNA have also been seen in biopsies taken from patients with objectively proven persistent OD.[51]

Persistent inflammation may not only suppress stem cell regeneration but likely also account for the downregulation of olfactory receptors and signaling genes in the ORNs that has been demonstrated in animal models.[52] Fluctuations in receptor expression may help to explain the fluctuating nature of olfactory loss that has been anecdotally described. While perhaps more true for hyposmia, a decrease in number of correctly functioning olfactory neurons may also lead to a mischaracterization of odors as seen in parosmia.[53]

LIMITATIONS OF STUDIES ASSESSING RECOVERY

With the exception of the COVID Challenge trial[22] all studies are limited by the lack of baseline olfactory assessment before infection. Longitudinal studies need to account for the background prevalence of hyposmia in a healthy population being nearly 20%.[54]

Some studies have attempted to account for this by asking patients to recall and retrospectively rate their olfactory function before infection.[55] However, this approach has significant limitations, as across many fields of medicine, patients have been found to exaggerate both positive and negative features when asked to retrospectively rate their symptoms—they, therefore, may neglect pre-existing mild abnormalities in the face of sudden loss of olfactory function.

Boscolo-Rizzo et al.[21] aimed to correct for pre-existing OD by undertaking an age and gender-matched-pair case-control study. The psychophysical assessment of chemosensory function took place after a median of 401 days from the first SARS-CoV-2 positive swab. The evaluation of orthonasal smell identified 46% and 10% of cases and controls, respectively, having olfactory dysfunction. Testing of gustatory function revealed that 27% of cases, compared to 10% of controls, showed gustatory impairment. This study highlights the importance of considering the impact of pre-existing OD in studies with less rigorous methodology.

LIMITATIONS OF THIS REVIEW

Our initial search identified more than 10,000 papers. We have not undertaken a formal systematic review but searched titles only for papers assessing recovery beyond 6 months after infection, to supplement the meta-analysis of Tan et al.[2] As a result, we may not have included all case series reporting long-term recovery and have not included a PRISMA diagram to avoid misleading the reader into thinking this is a systematic review. The literature is rapidly evolving and there are studies published beyond our initial search.

COUNSELLING FOR PATIENTS WITH LONG-TERM CD

There remains a gap in the knowledge of therapeutic options for long-term olfactory dysfunction following COVID-19 infection.[56] Where studies exist, most focus on evaluating the effectiveness of interventions given during and shortly after acute infections, excluding patients with more persistent loss.

OT has been discussed in the literature as a potential therapeutic option for anosmia.[57] This treatment consists of exposing the patient to a range of specific odors and encouraging them to sniff the scents multiple times a day, and can be performed using household items like coffee, or essential oils. The aim of OT is to enhance detection of smell by stimulating olfactory neurons.[3] OT has shown promise in promoting the recovery of olfactory function in various circumstances, including postviral conditions.[3,58]

Olfactory dysfunction after COVID has been shown to be associated with a reduction in volume in the olfactory cortex on magnetic resonance imaging and aberrant olfactory functional connectivity.[59] By comparing magnetic resonance imaging before and after SARS-CoV-2 infection, brain-related abnormalities mainly affecting the limbic and olfactory cortical systems were observed.[27] However, these alterations were interpreted as the consequence of repeated olfactory sensory deprivation rather than the cause of smell loss, leading to a loss of gray matter in these olfactory-related brain regions.[60] In contrast, OT has been shown to reorganize functional connectivity[61] and increases gray matter volume in the olfactory cortex.[62]

In light of no other meaningful treatments, OT should still be considered when discussing treatment options with patients with long-term olfactory dysfunction following COVID-19 to potentially enhance recovery, as extended training has been shown to benefit over 9 months compared with a control group.[63]

The importance of psychological support for patients with long-term CD should not be undermined. Analysis of a COVID-19

Facebook support group allowed the investigators to understand the true psychological impact of smell and taste dysfunction.[8] Many participants were struggling with both physical and mental health results of loss of smell and taste, such as managing personal hygiene, loss of appetite, weight loss, anxiety and depression.[8] Where possible, healthcare professionals should direct such patients to appropriate mental health support such as therapy or counselling, to create a safe space to express anxieties related to their altered chemosensory experiences. In addition, awareness of the growing online platforms, with social media self-help groups and expert run charities that offer professional guidance and up-to-date resources relating to olfactory dysfunction, such as Abscent and Fifth Sense, should be encouraged.

Our understanding of long-term CD post-COVID-19 infection is continuously evolving. As time progresses, recovery stories from more than 2 and sometimes 3 years after onset continue to be posted on social media and emerge in the literature.[37] These suggest that patients can remain hopeful, and physicians should avoid informing patients that their loss is permanent.

Novel therapies for olfactory dysfunction are currently being investigated, such as stem cell therapy, olfactory epithelium transplantation, and electrical stimulation.[64] These innovative trials also offer participating patients with long-term CD an opportunity to contribute to the advancement of knowledge and potentially access innovative treatments.

CONCLUSION

Chemosensory dysfunction post-COVID-19 continues to blight the lives of millions of people around the world. The majority will achieve complete recovery within 6 months and for those who do not, there is evidence that recovery can occur even after years pass from initial infection. A better understanding of the risk factors, pathophysiology, and disease trajectory will help equip healthcare providers to tailor their support for affected individuals. Further research is needed to elucidate the underlying mechanisms of CD which may lead to breakthroughs in targeted therapies.

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Melanie Dias and Zara Shaida researched and cowrote the majority of the text with supervision, editing, and proofreading from Nora Haloob and Claire Hopkins.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data was created or analyzed in this study.

ETHICS STATEMENT

The authors have nothing to report.

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