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# Insight into the mechanisms of olfactory dysfunction by COVID-19

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ABSTRACT

One of the unique symptoms of COVID-19 is chemosensory dysfunction. Almost three years since the beginning of the pandemic of COVID-19, there have been many studies on the symptoms, progress, and possible causes, and also studies on methods that may facilitate recovery of the senses. Studies have shown that some people recover their senses even within a couple of weeks whereas there are other patients that fail to recover chemosensory functions fully for several months and some never fully recover. Here we summarize the symptoms and the progress, and then review the papers on the causation as well as the treatments that may help facilitate the recovery of the symptoms. Depending on the differences in the levels of severity and the locations where the main pathological venues are, what is most effective in facilitating recovery can vary largely across patients and thus may require individualized strategies for each patient. The goal of this paper is to provide some thoughts on these choices depending on the differences in the causes and severity.



## 1. Introduction

It has been almost three years since the beginning of the outbreak of COVID-19. The world has gone through a tragic pandemic that has killed over 6.49 million people worldwide with an official record of over 604 million cases as of September 2022. In the United States alone, the number of deaths surpassed one million, which is more than 15% of the overall deaths worldwide. The symptoms are broad; from coughs, fever, headaches, shortness of breaths to the unique symptoms of chemosensory dysfunction (losing the sense of smell, *i.e.*, anosmia, and/or the sense of taste, *i.e.*, ageusia) [1–3].

The unique symptoms of chemosensory dysfunctions and the mechanisms with which the virus enters host cells and travels along the body system have been studied extensively during these almost three years by scientists around the world. There is evidence for several possible causes of chemosensory dysfunction due to COVID-19, which suggests there can be multiple differences across patients. Here, we summarize the symptoms, the progress of the symptoms, the possible causes, the chemical compounds that often trigger sensing altered smell, and the studies on the various treatments that may help facilitate the recovery from chemosensory dysfunction.

## 2. Epidemiology of COVID-19 induced chemosensory dysfunction

### *2.1. Olfactory dysfunction due to COVID-19: the numbers and symptoms*

Typical course of COVID-19 starts with common cold-like symptoms (for example, fever, cough, sputum, sore throat, and

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nasal discharge) and malaise, and abnormal sense of smell and taste appear approximately 5 days on average (range 1-14 days) after infection. These cold-like symptoms last about one week [4]. Some patients have gastrointestinal symptoms such as nausea and diarrhea as well, and some patients remain asymptomatic [1–3,5]. Among the various clinical manifestations of COVID-19, sensory dysfunction is particularly characterized with a higher prevalence compared to other viral infections [1,5–7]; new onset of smell and/or taste disorders were significantly more frequent among COVID-19 patients (39%) than influenza patients (13%) [8].

The COVID-19-induced olfactory and taste dysfunctions are so unique that they are considered to be one of the diagnostic markers of COVID-19. This is based on 1) the high percentage of the patients that exhibit the symptoms [8–11], 2) the early onset of these symptoms compared to other symptoms [11], and also 3) because for some patients they are the only symptom of COVID-19 [1,12]. The incidence of olfactory dysfunction and taste dysfunction ranges 32-87% and 35-89%, respectively, with a concomitant incidence of olfactory and taste dysfunctions reported to be about 35% [9,10] (As the number of cases of taste dysfunction, especially of the self-reported ones, highly likely include impaired flavor perception due to olfactory impairment, the number of cases of actual taste dysfunction is most likely less than the numbers reported). About 10% of the patients had olfactory and taste dysfunctions preceding the onset of other symptoms, and there have been many patients not even showing other symptoms. The asymptomatic carriers of the virus may have contributed to the spread of COVID-19 without knowing they were infected [1,12].

Olfactory dysfunction is more prevalent in females compared to males and is more common in the younger age groups between 20 to 40 years old [1,2,8,12]. There are differences in the incidences of olfactory dysfunction depending on geographic areas as well. In Western countries, the prevalence of olfactory dysfunction is over 50%, while in Asian countries it is only about 30%. This suggests the possibility of genetic differences in the vulnerability to contract the virus [13,14], cultural differences in accepting to wear masks and other face coverings in public [15], or other factors like cultural differences in the eating and drinking habits of materials that contain phytochemicals with beneficial effects against the virus [16].

Symptoms of olfactory dysfunction include anosmia (complete lack of olfactory sense), hyposmia (reduced olfactory sense), parosmia (distorted olfactory sense), and phantosmia (sensing odors that don't exist). Anosmia seems to be more common than hyposmia in COVID-19 patients [9,10]. Patients with olfactory dysfunction due to COVID-19 often experience parosmia and the distorted smell is often "smoky" or "burnt odor" [1,7]. Parosmia is often observed in patients who had olfactory dysfunction, for example, in conventional post-viral olfactory dysfunction (PVOD) and it is not unique to COVID-19-induced olfactory dysfunction [16]. We will discuss parosmia in more detail later in this review.

SARS-CoV-2 showed rapid evolution, leading to the emergence of various variants, most notably the rampant Delta and Omicron variants, which differ in infectivity and clinical symptoms compared to the original lineages [17,18]. The Omicron variant shows less tissue damage to the olfactory neuroepithelium [19] and a lower incidence of olfactory dysfunction compared to the original lineages [20], although it still ranges from 5.8 to 32.5% [20,21].

### *2.2. Recovering from COVID-19 induced chemosensory dysfunction*

Like other post-viral olfactory dysfunctions, the symptoms of chemosensory dysfunction caused by COVID-19 persist for a long term in some patients. In a study in the UK that conducted two surveys to the same participants, 86.4% of the COVID-19 patients had anosmia and 11.5% had hyposmia at the first survey, which was completed 1 to 2 weeks after the onset of COVID-19 [22]. At the second survey one week later, 80.1% of the patients showed improvement, whereas 17.3% of the patients showed no change [22]. In a longer-term follow-up study by Ferreli et al. (2022) [23], more than 80% of the patients with COVID-19-induced olfactory dysfunction reported complete recovery of olfactory within the first three months. In the same study, 87% of the patients reported complete recovery of the smell function after 18 months. The severity of chemosensory impairment at the onset was reported to negatively correlate with recovery, *i.e.*, the more severe the initial symptoms, the longer it took to regain the olfactory sense [23]. The patients who showed improvements in the olfactory function within the 7 days after contracting COVID-19 also showed early recovery [23].

However, there are studies reporting higher incidences of persisting olfactory dysfunction (5-60%) 2 to 6 months after the onset of the symptom [24–28]. A high percentage of healthcare workers who had mild COVID-19 still had olfactory dysfunction (52%) 5 months post-COVID-19 [29]. Niklassen. et al (2021) [28] reported that 26% of the patients still had some olfactory dysfunction 2 months post-COVID-19, although others recovered within one month of the onset. While many patients with long-lasting (long-haul) COVID-19 have persistent olfactory dysfunction, very few studies provide a prognosis for possible time to recovery. Even after 6 months to a year post-COVID-19, approximately 25 to 30% of patients still suffer from persistent subjective olfactory dysfunction [29–31]. Ohla et al. (2022) [32] reported that half of the patients felt their olfactory sense was less than 80% of their pre-COVID-19 status [32].

Some studies have measured and compared the levels of severity in the olfactory dysfunction of COVID-19 patients with negative controls and found a higher prevalence of olfactory dysfunction in the former group one year after contracting COVID-19 [33,34]. The Global Consortium for Chemosensory Research (GCCR) investigated parosmia/phantosmia and reported that, less than 10% of patients had parosmia/phantosmia during the early stages of infection, which rose to 47% having parosmia and 25% having phantosmia after 2-10 months [32]. In addition, 56.7% of the patients who still had olfactory dysfunction 11 months post-COVID had parosmia and 28.0% of them had phantosmia

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[29]. During the infection, the frequency is 16.9% and 22.9%, respectively, both of which are more frequent [29].

## 3. Possible causes of olfactory dysfunction

During the two years since the COVID-19 pandemic started, many papers on the possible causes of COVID-19-induced chemosensory dysfunction have been published. As early as in spring 2020, papers showing that angiotensin converting enzyme-2 (ACE2), which has been known as the entry receptor of SARS-CoV-2 [35,36], is not expressed in the mouse olfactory sensory neurons but is expressed in the supporting cells in the olfactory epithelium were published [37,38]. Transmembrane protease serine 2 (TMPRSS2), which primes the spike protein of SARS-CoV-2, and furin, which facilitates spike protein cleavage, were both missing in the olfactory sensory neurons [38]. This first suggested that the chemosensory dysfunction is not due to the damage in the olfactory sensory neurons themselves as the virus won't enter them without the ACE2, TMPRSS2, and furin. However, later studies using hamsters have shown that infection can cause complete morphological damage to the olfactory epithelium, not only to the supporting cells but including the olfactory sensory neurons [39]. They have also shown that, in the olfactory mucosa samples from COVID-19 patients and olfactory mucosa tissue samples from hamsters, cells positive for olfactory marker proteins (OMP) overlapped with immunostaining of SARS-CoV-2 antigens [39]. Later on, several other proteins have been found to have binding affinity with the receptor binding domain (RBD) of the spike protein (S-protein) of SARS-CoV-2, and facilitate the entry of the virus into the cells. For example, neuropilin-1 (NRP-1) is known to bind to the S-protein of SARS-CoV-2, and NRP-1 is expressed profoundly in the olfactory epithelium [36,40]. Sialic acid is also known to mediate binding of the virus to host cells, and facilitate entry of the virus [41,42].

Other than the multiple types of proteins that serve as receptors or those that facilitate the entries, there are also other factors that can become involved in worsening the symptoms. Studies using brain organoids have shown that the SARS-CoV-2 negative cells around the SARS-CoV-2 positive cells show upregulation of pathways related to the cellular responses to decreased oxygen levels (hypoxia), whereas the infected cells showed gene expressions typical to excess supply of oxygen (hyperoxia) [43]. These studies suggest that even if the olfactory sensory neurons were not infected by SARS-CoV-2, the hypoxic environment may weaken them and may cause apoptosis, which can cause damage in the olfactory membrane.

Infection can cause inflammation, *i.e.*, the release of proinflammatory cytokines, and this can weaken the signaling from the olfactory epithelium to the olfactory bulb, and from olfactory bulb to regions in the brain related to olfactory sense. A new paper published in June 2022 has shown that inflammation can be the key factor in the lingering symptoms of long COVID, including long term chemosensory dysfunction [44]. They have shown using hamsters and humans that SARS-CoV-2 causes long-term injury to the tissues and organs with persisting activation of myeloid, T cells, proinflammatory cytokines and interferons even after the acute stage and without detectable virus [44]. De Melo et al. [39] have also shown that even after over 100 days post-infection, some post-COVID-19 patients still had viral load in the olfactory mucosa [39], suggesting that persisting virus or particles of virus might be involved in causing inflammation, which can weaken the olfactory function.

Recent studies have proposed new hypotheses on the mechanisms of COVID-19-induced chemosensory dysfunction. Hernandez-Clavijo et al. [45] have shown that the supporting cells of olfactory epithelium co-expressed ACE2 and transmembrane protein 16F (TMEM16F), which is a membrane protein involved in translocation of phosphatidylserine and is involved in syncytia formation. They suggested that large syncytia induced by cell-to-cell fusion can be involved in causing olfactory dysfunction. Syncytia, *i.e.*, fusion of neighboring cells, formation has had been observed in the lungs of COVID-19 patients. Buchrieser et al. (2020) [46] have shown that cells infected by SARS-CoV-2 can 'express the Spike protein at their surface' and bind to the ACE2 receptors of neighboring cells, causing cell-to-cell fusion and form large multinucleated syncytia [46–48]. TMEM16F is a calcium-activated scramblase involved in the fusion of the cells, and drugs that inhibit TMEM16F can suppress the fusion, thus suppress the syncytia formation [47]. This abnormal fusion, compared to normal fusion like fertilization, can facilitate the spread of infection to neighboring cells and damage the function of the cells. The expression of TMEM16F in the olfactory epithelium suggests that large syncytia induced by cell-to-cell can be involved in causing or facilitating olfactory dysfunction.

Changes in gene expression in the olfactory system have also been proposed to be involved in causing anosmia/hyposmia. Studies with humans and hamsters have shown that genes involved in olfactory signaling and olfactory receptor genes were downregulated [49], which can cause less functional olfactory sense because of the reduced expression of olfactory receptors and less functional olfactory signaling. In addition, recent studies have suggested the possible role of UDP-glucuronosyltransferase (UGT) [50]. UGT2A1 is expressed in the sustentacular cells and the cilia of sensory neurons in the olfactory epithelium and they are involved in odorant metabolization [51]. This odorant metabolization can suppress the olfactory sense by modulating the odorant chemical compounds into glucuronidated odorant metabolites, which don't activate olfactory receptors [51]. Thus, an upregulation of UGT2As could suppress the olfactory sensitivity. Shelton et al. [50] found from saliva samples that a genetic locus containing UGT2A1 and UGT2A2 on chromosome 4 (chr4q13.3) could be involved in the loss of the sense of smell and taste because of the significantly upregulated expression [50]. Although the mechanisms that they are upregulated are unknown, the higher expression of them could function in suppressing the olfactory system at peripheral level.

In addition to causes at the peripheral level, there are also reports on pathologies in the brain [52–54]. In a study with

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human subjects, paranasal sinus CT scanning and MRI of patients with persistent COVID-19-induced olfactory dysfunction revealed that 43.5% of the patients had a significantly lower volume in the olfactory bulb [52]. In addition, in 54.2% of the patients, there were changes in the shape of the olfactory bulb, and the signal intensity was abnormal in 91.3% of the patients [52].

SARS-CoV-2 can travel from peripheral locations to the brain [55]. Ueha et al. [55] demonstrated that inoculation of SARS-CoV-2 in the oral cavity of hamsters spread to the central nervous system through the nasal cavity. Studies which inoculated SARS-CoV-2 into the nostrils of mice have also found that the virus reached to the olfactory bulb and other regions in the brain, as well as lung, eye, kidney, spleen, pancreas, heart, and liver tissues in a day [43,53]. Importantly, TUNEL staining of the brain tissues have revealed that there were a significantly high number of apoptotic cells in the brain [43,53]. Similarly, in a study using rhesus monkeys, exposure to SARS-CoV-2 by aerosol inhalation or a multi-route mucosal infection (through conjunctival, nasal, pharyngeal, intratracheal routes) caused neuroinflammation, microhemorrhages, brain hypoxia, neuropathology, neuronal degeneration and apoptosis [56].

What these results suggest is that COVID-19-induced olfactory dysfunction can be caused by weakened signaling at the olfactory bulb and at the olfactory cortex. Further, the causation of COVID-19-induced olfactory dysfunction may have multiple sources, depending on the patient. Thus, which factor is the major cause of dysfunction could vary in different patients, resulting in large differences in the time length it takes to recover.

## 4. Chemical compounds involved in parosmia

Olfactory sense is a sensory system that detects and recognizes chemical compounds. The large number of different chemical compounds are differentially sensed by the specialized dedicated receptors which become activated only by certain types of chemical compounds. These receptors form the mechanisms by which we identify and distinguish smells and the varied receptors are the reason why chemical senses involve a large number of different receptor genes.

When patients lose their senses of olfaction (anosmia or hyposmia), they sometimes experience distorted smells/tastes and the smells/tastes that don't exist. The former is called parosmia and the latter is called phantosmia. Many patients who experience the distorted smell, and smells that don't exist, describe the distorted smells as containing 'ashes', 'smoke', or 'metallic' elements. A new study showed that there are specific types of chemical compounds that trigger these types of parosmia [57].

Parker and colleagues, the authors of the paper [57] mentioned above, noticed the possibility that some common chemical compounds may trigger parosmia when they saw the list of food/beverage items that caused parosmia (Parker, personal communication). They hypothesized that these chemical compounds could trigger parosmia. Prior to that study, there were several hypotheses about parosmia. For example, 1) damage in the olfactory epithelium caused a reduction in the number of functioning olfactory sensory neurons so that the inputs are 'incomplete' and the smell seems distorted [58]. 2) The regeneration process includes rewiring of the axons, which become misguided causing the distorted smell [59]. These early hypotheses did not consider that there are some more specific chemical compounds that may trigger parosmia. This hypothesis was a very innovative one that only a chemist might notice.

The chemical compounds found to trigger parosmia (see Table 1) were structurally grouped into four types: thiols, trisubstituted pyrazines, methoxypyrazines, and disulfides [57]. The ones that highly triggered parosmia were the chemical compounds with lower threshold concentration. 2-Furanmethanethiol, which showed the highest score in triggering parosmia, is known to have the smell of coffee and roasted meat, and it is insoluble in water (PubChem 7363; CAS 98-02-2; FEMA 2493; $C_5H_6OS$). An interesting description in PubChem is that it is an "extremely powerful and diffusive odor which on dilution becomes agreeable, coffee-like, caramellic-burnt, sweet", and insoluble in water. An intriguing part of this description is that this chemical compound has a 'burnt' smell. The second from the top chemical compound that triggered parosmia was 3-methyl-2-butene-1-thiol [57]. An intriguing part of the report on this chemical compound is that it is found to be the source of the 'skunk-like' smell of *cannabis* [60].

Table 1 shows the chemical compounds listed in Parker et al. [57] that are also included in PubChem. Most of the smells of these chemicals have the description frequently reported in parosmia, such as "toasted", "burnt", and "coffee". This suggests a possibility that parosmia is caused by recognizing specific chemical compound(s) of the smell of, for example, coffee or roasted meat. It is sensed distorted but actually it may not be 'distorted' and instead it could be partial or incomplete smell of the food/beverages. Smells/flavors of foods and beverages contain hundreds of chemical constituents. It is possible that, as Leopold (2002) [58] hypothesized, parosmia is caused by the limited number of functioning olfactory sensory neurons, and this also explains why it happens a few weeks to months after the damage in the olfactory epithelium occurred [61,62]. That is, it is maybe caused by the differences in the pace of recovery of the olfactory sensory neurons and such differences are causing sensing of a limited number of the types of odorants, and becomes recognized 'distorted'.

If parosmia is an 'incomplete' perception of the smell of the foods by sensing some chemical constituents among the whole odor profile, how can we explain phantosmia, which is sensing smell that doesn't exist. Is it a peripheral phenomenon, in which olfactory receptors become activated without the ligands? Is it caused by wrongly activated central neural system? Or, are the olfactory receptors activated by chemical compounds that are not their original ligands? We still don't have the answers to these questions yet.

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**Table 1.** Chemical compounds reported to cause parosmia in Parker et al. [57].

| | PubChem CID | CAS | FEMA | Molecular formula | Synonyms | Smell/flavor | MW | solubility |
|---|---|---|---|---|---|---|---|---|
| 2-Furanmethanethiol | 7363 | 98-02-2 | 2493 | $C_5H_6OS$ | furan-2-ylmethanethiol; furfuryl mercaptan; 2-furylmethanethiol; furfuryl thiol; and others | coffee-like, caramellic-burnt, sweet (PubChem); disagreeable unpleasant at high concentration (Acros Organics, ACC#34573); coffee roasted meat (FEMA 2493) | 114.17 | Insoluble in water |
| 3-Methyl-2-butene-1-thiol | 146586 | 5287-45-6 | 3896 | $C_5H_{10}S$ | Prenylthiol; 3-methyl-2-butene-1-thiol; prenyl mercaptan; 3-methyl-2-buten-1-thiol; and others | almond, coffee, foxy, spice (FEMA 3896); skunk-like smell (Oswald et al. 2021)(60) | 102.20 | Insoluble in water |
| 2,3-diethyl-5-methylpyrazine | 28905 | 18138-04-0 | 3336 | $C_9H_{14}N_2$ | 2,3-diethyl-5-methyl-pyrazine; 2-methyl-5,6-diethylpyrazine | Nutty, roasted, vegetable odor (PubChem); earth, meat, potato, roast (FEMA 3336) | 150.22 | 6.7 ug/mL |
| 2-methyl-3-furanthiol | 34286 | 28588-74-1 | 3188 | C5H6OS | 2-methylfuran-3-thiol; 3-furanthiol; 2-methyl-3-furanethiol; and other | Roasted meat (PubChem); fried, nut, potato, roasted meat (FEMA 3188) | 114.17 | Insoluble in water |
| 2-ethyl-3,5-dimethylpyrazine | 26334 | 13925-07-0 | 3150; 3149 | C8H12N2 | 3,5-dimethyl-2-ethylpyrazine; 3-ethyl-2,6-dimethylpyrazine, 2,6-dimethyl-3-ethylpyrazine | Toasted nut, chocolaty, sweet woody odor (PubChem); burnt type odor; roasted cocoa or nuts (Burdock and Carabin 2008); earth, nut, potato, roast (FEMA 3150); broth, earth, potato, roast (FEMA 3149) | 136.19 | Soluble in water, oils, organic solvents |
| 2-isobutyl-3-methoxypyrazine | 32594 | 24683-00-9 | 3132 | C9H14N2O | 3-isobutyl-2-methoxypyrazine; 2-methoxy-3-(2-methylpropyl)pyrazine; 2-methoxy-3-isobutylpyrazine | Green bell pepper, green pea odor (PubChem); bell pepper, earth, green pepper, spice (FEMA 3132) | 166.22 | Soluble in water, organic solvents, oils |

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## 5. Treatments

### 5.1. Olfactory training

Since 2009, a series of studies showing the positive influences of inhaling chemical constituents of four different types of odors on facilitating recovery from ano/hyposmia have been published. The first group of studies focused on the major chemical constituent of the four different odors, *i.e.*, phenyl ethyl alcohol (PEA) representing rose, eugenol representing clove, citronellal representing lemon, and eucalyptol representing eucalyptus [63] (for review, see Koyama and Heinbockel, [64]). These four types of odors were selected based on the odor prism hypothesis proposed by Henning (1916) [65] and each odor represented flowery smells, (rose), fruity (lemon), aromatic (clove), and resinous (eucalyptus). Basically, the participants smelled each of the multiple types of odors twice daily and 15 to 20 sec for each odorant. This means that olfactory training is not just sniffing for a second to test whether they can sense the smell but it is more like thoroughly exposing the olfactory system to these chemical compounds. Higher concentration of the smell was found to have stronger effects, in particular with patients who started olfactory training within 12 months after the onset of the disorder [66], and longer periods of olfactory training resulted in better effects [67]. Using fMRI, it was found that olfactory training can facilitate the recovery of the volume of grey matter at the limbic system and the thalamus of the brain [68]. It was also found that increasing the variety of the types of odorants had stronger effects on improving the olfactory sense [69]. Patel et al. [70] reported that using the essential oils of rose, lemon, eucalyptus, and clove instead of the single types of odorants for the olfactory training was similarly effective. Using essential oils for olfactory training, and not using single types of odorants is now very common in the era that large number of COVID-19 patients have lost their sense of smell completely or partially.

In addition to the four types of odors commonly used in the olfactory training, some studies have shown the possibility that stimulating trigeminal nerves could be important in the recovery of olfactory sense [71]. Frasnelli et al. [71] have shown that patients who are showing recovery of olfactory sense showed an increase in the responses to irritants ($CO_2$ was used as stimulant) as well. Bensafi et al. [72] also reported that the presence of a trigeminal stimulus ($CO_2$) during odor encoding alters the neural representation of the pure odor. Oleszkiewicz et al. [73] has reported that trigeminal training using CO2 increases the self-rated nasal patency, which suggests that this can help if olfactory dysfunction is associated with nasal patency.

This olfactory training has been used not only in patients with olfactory dysfunction but also in healthy elderly people and children. In the elderly, it has the potential to delay the decrease in the sense of smell due to ageing, although it will not prevent a gradual loss [74]. In the children, not only the ability to identify the odor types was increased but also the threshold concentration to detect the odors that were not used in training became lower, indicating the higher sensitivity to odors in general [75]. This suggests that olfactory training has benefits in all age groups and not only for recovery from ano/hyposmia caused by COVID-19 and other post-viral olfactory dysfunction but also for healthy people, in enhancing olfactory sensitivity.

### 5.2. Supplements/medicines/herbal medicines

During over three years since the outbreak of COVID-19, an extensive amount of clinical data has been accumulated because of the uniquely high occurrence of chemosensory dysfunction. Despite such increase in the data, the treatment strategies for post-COVID-19 olfactory dysfunction (PCOD) are still limited, and current evidence supports only olfactory training as a first-line intervention [76–78]. A variety of drugs and supplements have been proposed for the treatment of non-conductive smell disorders, including post-viral olfactory dysfunction, such as, corticosteroids (systemic, topical), caroverine [79], theophylline [80], minocycline [81], insulin [82], tokishakuyakusan (herbal medicine) [83], sodium citrate [84], alpha-lipoic acid [85], vitamin A [86], and zinc [87–90], as some of the examples. Nevertheless, the effectiveness of most of these treatments remains uncertain.

Steroid therapy was initially considered negative due to concerns about the promotion of viral rebound and association with adverse events including acute respiratory distress syndrome [91]. However, at present, corticosteroids are likely the most effective drugs in reducing immunopathological damage [92]. Corticosteroids come in a variety of forms, including injectable steroids, oral steroids, nasal steroids, and nasal sprays. According to two consensuses [76,93], limited intranasal or oral corticosteroid course may be effective for patients with PCOD. Due to the multi-system nature of SARS-CoV2, multidimensional risk benefit analysis should occur before initiation of oral steroid therapy. Topical steroids include nasal drops, nasal irrigation, and intranasal corticosteroid sprays (ICS). Topical steroids may ameliorate olfactory impairment in patients with COVID-19, but it is unclear whether they contribute to full olfactory recovery [94]. Posture is also important when using nasal steroid drops, and the Kaiteki position [95] (Fig. 1) may help the steroids to reach the olfactory cleft, facilitating the drug's effect. While nasal irrigation, rather than ICS, may be more effective at treating PCOD due to increased penetration to the olfactory cleft [96], the current consensus is that ICS should be used for patients with PCOD symptoms lasting longer than 2 weeks [76,93].

Some studies suggest that experiencing a variety of food textures [97] may have indirect effects on facilitating recovery from olfactory dysfunction. The senses of smell and taste are involved in the pleasure of eating and cooking. Patients with chemosensory dysfunction often lose appetite and decrease nutritional intake which can affect their recovery. The process of eating foods with different textures may stimulate a variety of different sensory modality, and such stimulation may have positive influences on patients with anosmia [97,98]. Harder foods require longer time to chew and ingest, and the hard textures may stimulate trigeminal nerves [97].

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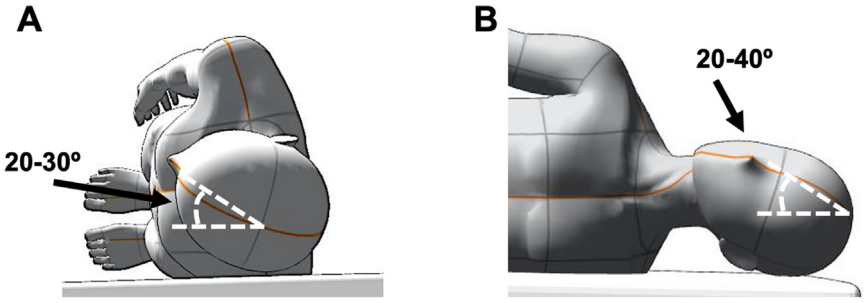


**Fig. 1.** Kaiteki position (a kind gift from Dr. Yuko Yamanaka, drawn based on the figure in [95]). To administer nasal drops to the right nostril, let the patient lie down with the left side down and turn the neck and the head to the right about 20 to 30° (A), and then tilt the head down making the jaw up about 20 to 40° (B) so that the right nostril slightly faces up. For the left nostril, let the patient lie down with the right side down, turn the neck and the head to the left 30°, and tilt the head down 30° so that the left nostril slightly faces up. 'Kaiteki' means comfortable in Japanese language.

In summary, the most effective treatment for PCOD at present is olfactory training, and no other treatments as effective as olfactory treatment have been identified so far. Combinations of olfactory training and ICD may be more therapeutic than olfactory training alone. Additional study is required to define specific treatment recommendations and expected outcomes for PVOD in the setting of COVID-19.

## 6. Conclusion: what is next

Although post-viral chemosensory dysfunction has been known for decades, COVID-19 has extremely increased the number of patients with chemosensory dysfunction. What we can see by reviewing the studies published during these several years is that the causation and the level of severity can be different depending on the patient. Such differences suggest that the strategy of treatment would require adjustments depending on these differences in order to expect it to bring improvements effectively. This could be the time to develop a treatment strategy based on such differences to provide a 'precision medicine' that matches the needs of each patient.

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