Review

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A Review on the Epidemiology and Mechanism of Actions of Olfactory Dysfunction as a Sequela of SARS-CoV-2 Infection

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Review

A Review on the Epidemiology and Mechanism of Actions of Olfactory Dysfunction as a Sequela of SARS-CoV-2 Infection

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Abstract: At present Coronavirus disease-2019 (COVID-19) is one of the leading contributing factor to mortality and the impact of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection on the sinonasal tract has become more prominent, particularly with the rising awareness of olfactory dysfunction (OD). We extracted data from published papers available in electronic databases (Wiley online library, PubMed, and Nature). We used the following search terms alone or with combinations - Olfactory dysfunction, SARS-CoV-2, mechanism and treatments. We found worldwide up to 98% of patients confirmed OD due to COVID-19. Current studies have implied that regardless of the high self-reported recovery rate, 25–40% of patients after 1 or 2 months and approximately 15%–28% of patients at six months struggle to fully restore their sense of smell. Moreover, female sex, younger and older age, active smoking, and chronic lung disease are reported as the associated risk factors of OD. Although the pathophysiological mechanism of action(s) of the OD is yet to be explored in depth, central nervous system (CNS) entrance, olfactory bulb (OB) and sustentacular cell damage, neural routes inflammation, non-neuronal cells damage, decreased OB volume and deregulation of olfactory receptor genes are among the commonly reported mechanisms for the development of OD.

Keywords: COVID-19; SARS-CoV-2; mechanism of action; smell loss; olfactory dysfunction; anosmia; treatment

1. Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) triggers the respiratory viral infection known as Coronavirus disease-2019 (COVID-19) [1]. The first COVID-19 case was identified in December 2019 in Wuhan, China [2] and rapidly spreading worldwide [1,3]. As of July 2023, approximately 767 million COVID-19 cases were confirmed while more than 6.9 million people died globally (https://covid19.who.int/). The term "post-acute sequela of SARS-CoV-2 infection" (PASC) covers a wide spectrum of multi-systemic symptoms which appear 4 or more weeks after infection, regardless of infection severity [4]. These symptoms last more than 24 weeks or 6 months [5,6]. Among all the sequelae, one emerging global health concern is persistent post-viral olfactory dysfunction (OD) [7]. Although many patients recover spontaneously from their OD [8], persistent smell loss is typically the most common post-viral symptoms which are seriously impacting the quality of life [8–10].

Persistent OD symptoms include complete lack of olfactory sense (Anosmia), reduced olfactory sense (Hyposmia), distorted olfactory sense (Parosmia), and sensing odors that do not exist (Phantosmia) [11]. Among all symptoms, patients with Parosmia reported a distorted smell commonly described as a "smoky or burnt odor" [12,13]. Parosmia is prevalent among patients with OD, such as conventional post-viral OD, and is less likely to happen in COVID-19-induced OD [11,14]. Statistics from the first wave of the COVID-19 in 2020 reported smell loss in 5-85% of individual afflicted with the SARS-CoV-2 virus based on mild and severe cases [15–24], however, a comprehensive meta-analysis decreased the figure to 77% using objective olfactory function tests

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method [25]. Intriguingly, study by Chiesa-Estomba et al. (2020) reported that most people quickly recover their sense of smell within 10 ± 6 days as smell restoration was as rapid as its loss [26]. However, newer data on OD have suggested that 25-40% of patients after 1-2 months [27,28] and around 15%-28% of patients after 6 months [28,29] do not completely restore their sense of smell. Additionally, patients with COVID-19 also frequently report alterations to their sense of smell which is 40–50% of people on average, globally [15,30]. When objectively assessed, up to 98% of patients confirm OD [31].

Recently, Butowt et al. (2023) reported that the degeneration of support cells which are infected in the olfactory epithelium (OE) induces altered mucus composition and retraction of the cilia on olfactory receptor neurons [32]. Additionally, Chee et al. (2023) explained there are variations in susceptibility to the key receptors necessary virus to enter, angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) across various populations of people and different SARS-CoV-2 variants [33]. Karimian et al. (2022) also mentioned that TMPRSS2 may facilitate OD [34]. However, an in-depth study of all possible mechanism of action is yet to be reported. Current literature review scrutinizes the novel cellular and molecular mechanism of actions involved in persistent OD induced by SARS-CoV-2. We pointed out the risk factors associated with persistent OD. We also discuss the prevalence, recent treatments along with different chemical compounds to treat OD as PASC in the future. In addition to that, we also explore the limitations, potential OD-induced diseases, and future perspectives.

2. Epidemiology of Persistent OD Induced by COVID-19

The COVID-19-induced OD is considered as a specific indicator of COVID-19 diagnosis since i) a high percentage of patients possess the symptoms [35–38], ii) is the earliest symptom compared to other symptoms, and iii) in some patients with COVID-19, it appears as the only symptom [12,23]. Persistent OD is found to be more common in patients infected with wild-type SARS-CoV-2 and less common in Omicron and Delta variants (B.1.617.2) infected patients [39,40]. The possible reason suggested by National Institute of Infectious Diseases that the viral RNA amount decreases after six days of infections and no detection of infectious virus since diagnosis or symptom after 10 days (https://www.niid.go.jp/niid/en/2019-ncov-e/10884-covid19-66-en.html). The incidence of COVID-19-induced OD ranges from 32-87% [36,37]. However, it affects 50-75% of the individuals who are diagnosed with COVID-19 in the acute stage [23,41,42].

3. Role of Host Factors in OD

COVID-19-induced OD is more prevalent among young adults (ranging from 20-40 years old), women, and people with relatively mild disease [43–45]. Compared to male patients, female patients were more inclined to have persistent OD symptoms [29,46–49]. Possible reasons could be explained by the findings that women have more cells than men in the olfactory bulb (OB) which is a dedicated part of the brain for olfaction [50]. Moreover, several studies [51–54] have found that women have higher odor-identification abilities than men. The female endocrine system and the impact of estrogen on the perception of smell have also been discussed as possible explanations for gender variations in olfactory performance [52,55]. However, no significant gender differences in intranasal volume have been reported [56,57].

The distribution of OD varies by geographic area as well. The prevalence of OD in Western countries exceeds 50%, whereas it is only about 30% in Asian countries suggesting the role of host genetics in the development of OD [58,59]. Other cultural habits of Asian people including- using masks and other face coverings in public [60], and eating and drinking materials containing phytochemicals with antiviral effects may also explain higher prevalence of OD among them.

4. Association of Different Variants of SARS-CoV-2 with OD

Prevalence of persistent OD varies within different variants of SARS-CoV-2 [61]. First, the so-called wild type was first overtaken by B.1.1.7 (a variant of concern (VOC) alpha) at the starting of

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2021, but it was rapidly supplanted by the considerably more deadly B.1.1617.2 (VOC delta); however, B.1.1.529 (VOC omicron), which was not discovered until late in November 2021, has already propagated globally [62]. According to a study by Vaira et al. (2022), self-reported olfactory loss occurs in 72.4%, 75.4%, 65.6%, and 18.1% of cases of the D614G mutation group, Alpha group, Delta group, and Omicron group, respectively. Additionally, psychophysical testing showed that the prevalence of OD in the D614G mutation group, Alpha, Delta, and Omicron groups, was 80.6%, 83.0%, 65.6%, and 36.3%, respectively and there were no statistically significant variations between the D614G, Alpha, and Delta groups [63]. According to epidemiological research where factors including age, gender, and co-morbidities showed the frequency of OD was lowest among Omicron variations, then the Delta variant, and finally the Alpha variant [62,64,65]. Numerous individuals who had minor COVID-19 infections throughout both Gamma and Omicron waves had a lower rate of reporting OD than individuals who had infections at the time of the initial lineages, according to Cardoso et al. (2022) (original lineages 52.6%, Alpha 29.0%, Gamma 27.5%, Delta 41.2%, Omicron 5.8%) (Figure 1) [33,64,66].

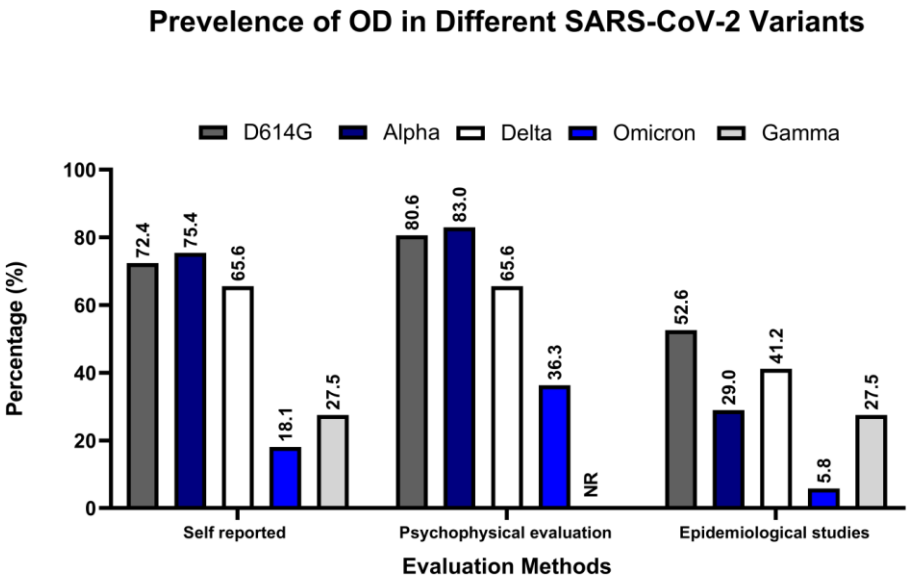

Figure 1. Prevalence of OD by different evaluation methods in SARS-CoV-2 variants. No data regarding VOC Gamma in psychophysical evaluation was reported. OD, Olfactory dysfunction; VOC, Variant of concern; NR, Not reported.

5. Risk Factors of OD

Considering the persistent nature of OD in a significant percentage of people even after two years of disease onset, it is critical measuring the clinical as well as the demographic factors linked to OD in COVID-19 patients. There are some debates about the age and persistence of OD in COVID-19. Studies by Nalbandian et al. (2021) and Groff et al. (2021) identified a connection between age and the occurrence of OD in prolonged COVID-19 [67,68]. However, increased co-morbidities and prescription drugs in elderly individuals could additionally impact the clinical course of OD [69,70]. Additionally, fever, cough, expectoration, stuffy nose, nasal congestion, purulent nasal, sore throat, foul breath, and xerostomia (oral dryness) are typical symptoms observed in patients with OD and patients who have suffered from three or more upper respiratory symptoms were prone to experience OD [71].

Based on the findings of multivariate analysis, risk factors associated with reporting a loss of smell were younger age [67,68], asthma [72], emphysema [73], female sex [29,46–49], or cough [49,71,74]. A clinical risk category approach by Johnson et al. (2022) [72], revealed the high-risk patients and individuals who were most likely to get serious infections and poor clinical outcomes. Moreover, age elder than 65 years, chronic lung disease (e.g. chronic obstructive pulmonary disease

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, idiopathic pulmonary fibrosis, asthma, liver cirrhosis, emphysema, cystic fibrosis, and bronchiectasis), active smoker, congestive heart failure, end-stage renal disease, active chemotherapy, history of diabetes or obesity with body mass index over 40 were considered to form this category [72]. The findings of different studies investigating the parameters of OD in epidemiological and clinical level are summarized in Table 1.

Table 1. Summary of different regions, patients, age, prevalence, recovery duration and other symptoms of OD.

Ref.	Study design and region	Number of Participants	Mean participant age (Year)	OD prevalence	Recovery duration	Common Symptoms
[49]	Systematic Review, Meta-Analysis; Europe, America, Asia	3699	30.0–55.8	3–11%	30–180 days	Cough, fatigue, rhinorrhea, sore throat, muscle, and joint pains.
[75]	Meta-analysis; Turkey	41	40.27 ± 14.5	45%	10–12 months	NR
[74]	Systematic reviews and meta-analysis; Europe, Asia, North America, and Australia.	10643	35–64	17%	>12 weeks	Fatigue, dyspnoea, myalgia, cough.
[76]	Systematic Review and Meta-Analysis.	16-91	34.3– 45.4	63%	2 months	Nasal obstruction, mucosal congestion.
[77]	Cohort, Case-control; North America, Europe, South America, Australia, and Africa, Asia.	42902	28–67	43.9%	NR	Headache and rhinorrhea.
[78]	A Multicenter Randomized Clinical Trial; Curitiba, Londrina, and Brazil.	80	36.7 ± 10.3	82.5%	1–2 weeks	Headache and nausea.

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[79]	Systematic reviews and meta-analysis; Turkey, The United Kingdom, Morocco, China, Spain, Italy, and the United States	3218	NR	26.9%	NR	Fever, dry cough, headache, dyspnoea, myalgia or arthralgia, fatigue, diarrhea, and vomiting.
[80]	Randomized double-blind placebo-controlled study; Iraq.	276	29	NR	1–4 weeks	Nasal obstruction, rhinorrhea, sneezing, and facial pain.
[81]	Observational, descriptive, and single-center study.	86	37.2	70.9%	2 weeks	Brain fog.
[82]	A multicenter real-life cohort study; London, United Kingdom, Padua, Italy.	44	40.5	81.8%	6–12 months	Nasal Obstruction and rhinorrhoea.
[83]	Prospective, cross-sectional; Aarau.	103	46.8	61.2%	NR	Nasal obstruction, cough, mucus production, rhinorrhea.
[25]	A systematic review and meta-analysis.	7,178	NR	98.3%	>2 weeks	Nasal obstruction, postnasal drip, or runny nose.
[84]	Meta-Analysis; Asia, Europe, Middle East East, Latin America, North America and Africa.	13,527	44– 52.7	51.4%	NR	NR
[85]	Systematic Review and Meta-analysis; North America, Europe, and Asia.	1627	36.9– 61.6	52.73%	NR	Nasal congestion, Peripheral nervous system complications, taste impairment.

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[86]	Meta-analysis; France, Italy, China, Iran, Singapore, USA, Germany.	1,354	34 –65	61.3%	NR	Fever, myalgia, chills, dyspnea, sore throat, cough.

Ref., References; NR, Not reported; OD, Olfactory dysfunction.

6. Pathophysiological Mechanisms of Actions of OD

SARS-CoV-2 penetrates the host system by connecting to two key receptors ACE2 and TMPRSS2 [87]. The OE contains a significant amount of ACE2 and TMPRSS2 receptors, particularly in sustentacular non-neural and neural stem cells [88,89]. Almost all Coronaviruses i.e. SARS-CoV [90], MERS-CoV [91], and HCoV-229E [92] are neuroinvasive. In case of COVID-19, ACE2 expression has been detected within olfactory neurons [93], suggesting that SARS-CoV-2 could affect the development of olfactory sense by entering the central nervous system through olfactory nerves [94]. The possible mechanism of action(s) is described below (Figure 2):

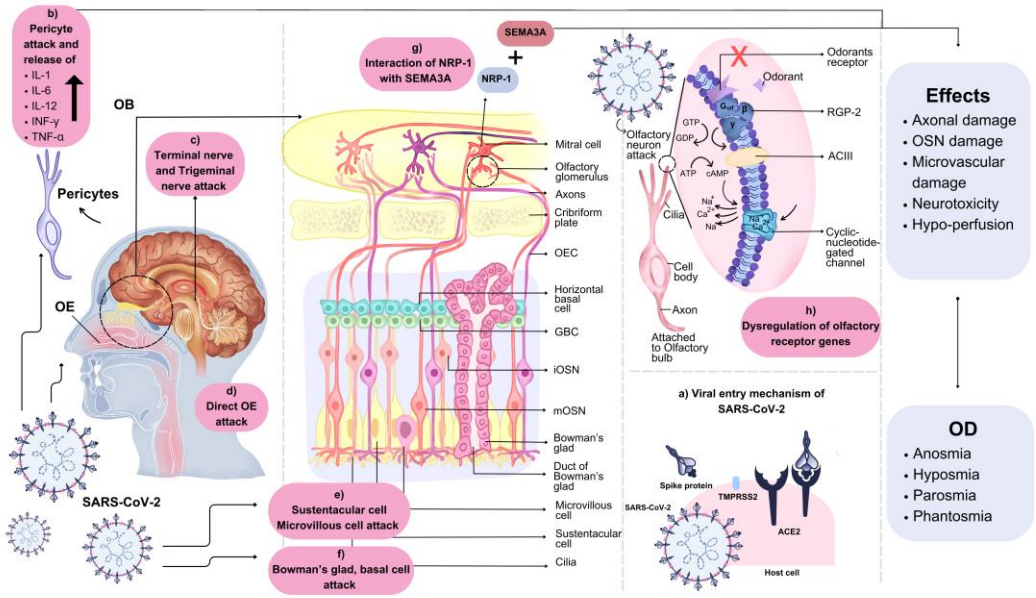

Figure 2. Mechanism of action(s) of OD. (**a**) SARS-CoV-2 binds to the ACE2 and TMPRSS2 receptor and enter host. (**b**) It attacks pericytes causing blood-brain barrier disruption due to IL-1, IL-6, IL-12, INF-y, and TNFα release; (**c**) Trigeminal nerve and terminal nerve attack by attaching to ACE2 and TMPRSS2 receptors present there; (**d**) or direct attack on OE; (**e**) Damage to OB and sustentacular cell; (**f**) Bowman's glands, basal cells, stem cells infections; (**g**) Interferes the interaction of NRP-1 with SEMA3A; (**h**) and lastly, dysregulates olfactory receptor gene. OD: Olfactory dysfunction; IL-1:Interleukin-; IL-6: Interleukin-6; IL-12: Interleukin-12; INF-y: Interferon-y; TNFα: Tumor necrosis factor-alpha; mOSN: Mature Olfactory sensory neurons; iOSN: Immature olfactory sensory neurons; ACIII: Adenylate cyclase III; OE: Olfactory epithelium; OB: Olfactory bulb; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; RGP-2: Regulator G protein signaling 2; NRP-1: Neuropilin-1; SEMA3A: Semaphorine-3A; OEC: Olfactory unsheating cell; GBC: Globose basal cell; TMPRSS2: Transmembrane serine protease 2; ACE2: Angiotensin-converting enzyme 2; ATP: Guanosine triphosphate; GDP: Guanosine diphosphate; cAMP: Cyclic adenosine monophosphate; OSN: Olfactory sensory neurons.

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6.1. Central Nervous System (CNS) Entrance

SARS-CoV-2 travels via axons within ensheathing or transneuronal cell to enter the host via CNS [95,96]. However, Neuropilin-1 (NRP-1), a trans-membrane glycoprotein functioning as a receptor for various ligands has been identified in the mitral cell of the OB, a region designated for smelling [97,98]. Mitral cells also express ACE2 and TMPRSS2 receptors and Neuropilin-1 has been implicated in viral retrograde axonal transport which may facilitate SARS-CoV-2 entry [98–100].

Additionally, interference of NRP-1 with semaphorine-3A (SEMA3A), a protein crucial for neuronal development [101,102], may lead to damage of axon and neuronal death eventually resulting in OD [103]. When SARS-CoV-2 enters pericytes, the blood-brain barrier is disrupted as a consequence of the production of many proinflammatory cytokines e.g. interferon-y (INF-y), interleukin-1 (IL-1), IL-6, IL-12, and tumor necrosis factor-alpha (TNFα) [104,105]. This subsequently leads to neurotoxicity, microvascular damage, and hypoperfusion to olfactory sensory neurons (OSNs), resulting in neuronal death and ultimately OD [106–110].

6.2. OB and Sustentacular Cell Damage

The transneuronal pathway of OSNs appears to be the quickest and most devastating route for SARS-CoV-2 to infect the OB [111,112]. Although, study by Khan et al. (2021) did not find evidence demonstrating the direct attack inflicted by SARS-CoV-2 on the olfactory route [113]. Direct damage is unlikely to be a factor in viral invasion since OSNs lack the ACE2 and TMPRSS2 required for SARS-CoV-2 entry [107,114]. Based on postmortem studies, sustentacular cells in the olfactory mucosa have been a primary target cell type with no data supporting the infection of OSNs in the OB parenchyma [113]. In sustentacular cells of the olfactory sensory epithelium (OSE), ACE2 expression occurs one hundred times greater than in the respiratory epithelium [115]. At the upper portion of the nasal canal, the increased expression of ACE2 may result in an unusually elevated viral load [116,117]. Consequently, leads to alteration to the olfactory pathway through sustentacular cell damage rather than direct damage on OSNs [118].

6.3. Neural Routes Inflammation

The terminal nerve (Nervus terminals or Cranial Nerve 0) and the trigeminal nerve are two nerves that run near the OB [119]. The trigeminal nerve forms an alternate pathway through CNS since the endings control the OE and branch to reach the OB [120–123]. Both nerves have ACE2 and TMPRSS2 receptors and packed ramification in the sinus cavities, OSE, and around the Cribriform plate [89,124]. Evidences suggest that SARS-CoV-2 compromises Gonadotropin-releasing hormone secreting neurons located in terminal nerve, implying the involvement of terminal nerve [125,126]. Additionally, every branch of the trigeminal nerve has been discovered to be carrying the virus. [127].

6.4. Non-Neuronal Cells Damage

SARS-CoV-2 infection can negatively influence non-neuronal cells in the olfactory sensory epithelium, such as Bowman's glands, basal cells, and stem cells which generate new OSNs and olfactory ensheathing cells [128,129]. Surprisingly, SARS-CoV-2 infection triggers significant death of cells and infiltration of immune cells, which immediately impairs the regularity of the OE structure and ultimately leading to OD [129]. Moreover, the origin of this infection is most likely to be peripheral indicating the short latency and rapid remission of COVID-19-induced OD [119].

6.5. Decreased OB Volume

Changes in the volume of OB may trigger persistent OD in COVID-19 and there have been multiple observations of decreased OB volume in COVID-19 patients with OD [130–132]. The virus invades the CNS by penetrating the interface of neural-mucosal within olfactory mucosa, and then passes through the designated neuroanatomical locations [127]. The OB volume may decrease during the chronic stage of COVID-19 due to neuroinflammation and neuroglial reaction triggered by direct SARS-CoV-2 virus damage to the OB and related neuroanatomical structures [131].

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6.6. Deregulation of Olfactory Receptor Genes

Infection with SARS-CoV-2 may elevate the expression of G protein signaling 2 (RGS2), a crucial regulator of odorant receptors [133]. Moreover, there was a considerable increase in RGS2 expression during the initial stages of infection, and it was highly linked with PTGS2- prostaglandin endoperoxide synthase 2, IL1B - Interleukin 1 Beta , CXCL8- C-X-C Motif Chemokine Ligand 8, NAMPT- Nicotinamide phosphoribosyltransferase, and other inflammatory markers [134]. These findings suggest that OD, especially Anosmia in COVID-19 patients may be caused by the upregulated RGS2 expression [135]. Additionally, RGS2 is hypothesized for the activatation of Golf, a Gsα-like G protein, upon odorant binding [136]. Golf-mediated Adenylate cyclase III (ACIII) activation boosts intracellular cyclic adenosine monophosphate (cAMP) levels, enabling a cyclic-nucleotide-gated channel to open. The passage of cations (Na+, Ca2+) via this channel results in an action potential generation, permiting the primary neuron to communicate with brain [137]. But SARS-CoV-2 may upregulate G protein leading to OD.

6.7. Drug-Induced OD

Zinc supplements are routinely prescribed during Covid-19 disease [138]. Study by Debbaneh et al. (2023) [139] reported zinc products and fluticasone propionate are found to be associated with OD, specifically reduced olfaction. Moreover, Varenicline and Fluticasone propionate are found to be linked to altered smell, although antineoplastic and immunomodulatory medications were responsible for 21.6% of olfactory adverse reactions and taken all of these together may indicate that drugs used during COVID-19 infections could give rise to OD [139].

7. Current Therapeutic Options

Researchers have recently discovered possible treatments for post-viral OD e.g. olfactory training [140–143], platelet-rich plasma [144–146], corticosteroid treatments [147–149], anti-neuroinflammatory therapy with co-ultra micronized palmitoylethanolamide with luteolin [150–153]. In addition, various medications and dietary supplements have been suggested for the treatment of non-conductive smell problems, including post-viral OD e.g. minocycline [154], theophylline [155], insulin [156] , caroverine [157], sodium citrate [158], alpha-lipoic acid [159], tokishakuyakusan (herbal medicine) [160], and vitamin A [161]. Nevertheless, the efficiency of most of these treatments remains unreliable.

Recently, a novel acellular secretome therapy (ST266) [162] and monoclonal antibodies [163,164] have gained attention for the future treatments of OD. ST266 is a novel biologic amnion-derived multipotent progenitor cells that contain secreted anti-inflammatory cytokines and growth factors [165,166] and monoclonal antibodies e.g. sarilumab appear to provide the best results with significant improvements in olfactory test measurements; however, high-quality trials with larger sample sizes are required for further analysis [167].

8. Limitations and Knowledge Gaps

Since the onset of the pandemic, significant progress has been conducted regarding comprehending sinonasal pathology in infection with SARS-CoV-2. Nevertheless, olfactory analysis is subjective and reviews are retroactive in nature [7,168,169], as a result the projection of the actual effect of OD may be inaccurate. Besides, a hypothesis linking the mechanism of actions and the development of OD to recovery rates has not yet been determined. Additionally, it is uncertain if the degree of smell loss and how rapidly it returns could be utilized to figure out the degree of severity a COVID-19 infection will be [170]. Understanding the real impact of the virus and improving the ability to forecast upper respiratory tract symptoms would also benefit from studies investigating molecular pathways, cytokine responses, and distinct SARS-CoV-2 variations at different stages of infection [171]. In addition, in-depth research is required to improve procedures for estimating the prevalence of sensory loss. Insights into the pathways causing OD in COVID-19 may shed light on other neurological symptoms reported in these patients [135].

9. Future Perspectives and Conclusions

Although OD is still a substantial and lasting side effect of the COVID-19 pandemic, more awareness can encourage research which facilitates the development of essential therapeutic alternatives. Recently, many individuals suffering from persistent OD reported decreased standards of life and display more signs of depression and anxiety [172,173]. Moreover, OD could trigger abnormal eating patterns e.g. higher consumption of sugar and salt or anorexia, which could lead to malnutrition and sudden weight loss [174,175]. Interestingly, OD has been one of the earliest symptoms of Parkinson's disease, Alzheimer's disease, and other Lewy body diseases [176–178]. Many of these diseases, which have started with OD, might progress to dementia [179,180]. Although it is not currently an effective diagnostic tool, the loss of olfactory function could influence the brain alterations which contribute to various disorders [176–178]. Further research is yet to be done to understand the mechanism of inducing different diseases by OD.

With numerous findings that emerged in the literature, clinicians must include a standard of care evaluation of olfactory function when treating individuals with a suspected or confirmed COVID-19 diagnosis. Regular in-home olfactory self-evaluation may be a useful place to start, given that psychophysical testing may not be feasible for many patients. In a nutshell, longitudinal evaluations of chemosensory function could assist in identifying individuals who may need further care and non-pharmacological therapies if they have a chronic olfactory impairment. In consideration of the growing significance of genetic variation for viral cell entrance and immune response to virus infection, future research must assess background of the genetic host which may impact the clinical phenotype as well as a response to vaccinations and medications [171].

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