<u>REVIEW ARTICLE</u>

Part Two: Perspectives on Olfactory and Gustatory Dysfunction Pathophysiology, Management, and Relevance to COVID-19: Current Approaches

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ABSTRACT

Context • The phenomena of olfactory and gustatory dysfunction disorders (OGD) are hardly unique to COVID-19. However, the widespread incidence of OGD as sequelae of COVID-19 has provoked rejuvenated interest in these long existing, but poorly studied maladies. **Objective** • This second of a three-part review discusses past and current approaches for treatment of OGD, not restricted to those that COVID-19 has caused, with the intention to lay a foundation for consideration of new paradigms for evaluation and management of OGD.

Design • The researcher performed a narrative review by searching databases including PubMed, Sciencedirect, Google Scholar, Old Dominion University Libraries, and the websites of various medical journals. Searches included numerous combinations of keywords accompanied by the phrases, loss of sense of smell and taste, olfactory and gustatory dysfunction disorders, as well as the terms

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Part one of this three-part review discussed the phenomena of olfactory and gustatory dysfunction disorders (OGD), which existed long prior to the emergence of COVID-19. Distortion of these senses, while insufficiently studied, is well known to be the consequence of numerous mechanisms, both infectious and noninfectious. However, the widespread incidence of OGD as sequelae of COVID-19 has provoked rejuvenated interest in these long existing, but poorly studied maladies, propelling OGD into being a major foci of research.

A paucity of evidence exists regarding OGD's mechanisms, and to an even lesser extent, its effective treatment. Past and recent studies have, for the most part, produced vague findings, and conclusions and recommendations for treatment anosmia, parosmia, ageusia, and parageusia. Such keywords included viruses, bacteria, fungi, protozoa, parasites, infection, COVID-19, treatments, medications, steroids, supplements, nutrients, alternative medicine, acupuncture, olfactory training, clinical trials, cranial nerves, pathogenesis, pathophysiology, and etiology. Setting • The Liebell Clinic, Virginia Beach, VA, USA Conclusions • The epidemiology and hypotheses of pathophysiology of post-COVID OGD has been addressed via numerous studies and reviews. However, extremely limited evidence of effective treatment for chronic OGD, in general, exists, Global demand for any treatment capable of reducing or resolving it is unprecedented. Past and present treatment approaches and recently initiated clinical trials, since the onset of the pandemic, have yet to yield any significant results. (Altern Ther Health Med. 2023;29(6):30-35).

have been insufficient. In short, consistently throughout the medical literature, no standard treatment has existed for OGD, nor have any approaches proven to be noteworthy, especially for chronic cases.

Types of OGD

Olfactory disorders. The types include: (1) anosmia, the complete loss of smell sensation; (2) hyposmia, reduced olfactory sense and discernment of scents; (3) parosmia, the distortion of the nature of scents, typically where otherwise pleasant or neutral scents are disagreeable; and (4) phantosmia, the phenomenon of olfactory hallucination—smelling something that isn't actually present.

Gustatory disorders. Alterations in gustatory sensation have similar medical terminologies: (1) ageusia, the complete loss of the taste sensation; (2) dysgeusia and parageusia, which are synonymous for abnormal or altered taste sensation that is often metallic in nature; and (3) phantogeusia, hallucination without the actual presence of taste stimuli. This article will generally refer to these collective phenomena as olfactory and gustatory dysfunction (OGD).

Pathophysiology of OGD

Researchers have written numerous reviews about OGD and have investigated the epidemiology, symptomatology, and hypotheses of the pathophysiology of OGD. Many have pondered how SARS-CoV-2 accesses the brain. An abundance of studies have analyzed the prevalence of post-COVID-19 OGD (PCOGD), as well as its distribution and patterns. Nevertheless, further review and investigation is unquestionably necessary. Researchers have never developed effective treatments, despite medical investigation throughout the ages, including current pursuits.

While the principal medical focus during the pandemic has rested on interventions intended for preventing COVID-19, its spread, amelioration of OGD, a common consequence of it, requires much attention. The global pandemic has galvanized the lay public, healthcare practitioners, and medical researchers. An expedient requirement for exploration of therapeutic and restorative treatment modalities is clear, on the broadest scale possible.

Part one of this three-part review addressed non-COVID-19 pathogens associated with OGD as well as known noninfectious causes, including mechanical, traumatic, chemical, aging, and neurodegenerative factors.¹ Understanding the pathophysiology and epidemiology of medical disorders serves as a cornerstone of public-health policy decisions. Such knowledge is influential in fostering the public availability of what are construed to be evidencebased treatment. The determination of the pathophysiology of PCOGD would lead to development of effect treatments.

With minimal redundancy, this second part of the threepart review intends to construct the framework for a new evidence-based paradigm that allows immediate consideration and investigation into efficacious treatment for PCOGD. Mere reiteration of the facts of this obviously existing problem would be of no value.

However, to date, this investigation has scarcely been the case. Part one of this three-part review also discussed the psychological implications of OGD. The public's lack of effective treatments fuels the desire for those afflicted by acute and chronic (post-) COVID symptoms to explore existing treatments that haven't necessarily been proven, studied, or FDA approved for such purposes. People seeking medications such as ivermectin and hydroxychloroquine, despite the lack of medical consensus about their efficacy, safety, or appropriate usage, exemplifies this desire.

Historically, researchers have very poorly considered dysfunction of taste and smell, which has contributed greatly to an ominous lack of medical preparation for the OGD consequences of the COVID-19 pandemic.

Part 2

It's pragmatic to employ existing approaches that perhaps researchers haven't considered but that have been useful for managing the effects of numerous other disorders. They might prove to be effective measures in response to the recently emerged illness. Too numerous to list, an abundance of studies have investigated smell and taste dysfunction during the COVID-19 infection. It would seem inarguable that a treatment capable of supporting natural restoration of olfactory and gustatory dysfunction would be of highest priority and of tremendous public interest to investigate, and offer to those in need. This would especially be the case if research has already established such a hypothetical intervention as safe and not cost prohibitive.

Part 2 discusses past and current approaches for treatment of OGD, not restricted to COVID-19. This article intends to lay a foundation for consideration of new paradigms for evaluation and management of OGD. It provides the background and rationale for investigating the potential of such a treatment, which part 3 will discuss in detail.

METHODS

Procedures

The researcher performed a narrative review by searching databases including PubMed, Sciencedirect, Google Scholar, Old Dominion University Libraries, and the websites of various medical journals written in English. Searches included numerous combinations of keywords accompanied by the phrases, loss of sense of smell and taste, olfactory and gustatory dysfunction disorders, as well as the terms anosmia, parosmia, ageusia, and parageusia. Such keywords COVID-19, treatments, medications, steroids, supplements, nutrients, alternative medicine, acupuncture, olfactory training, clinical trials, cranial nerves, pathogenesis, pathophysiology, and etiology. The setting was the Liebell Clinic, Virginia Beach, VA, USA. Inclusion criteria were any articles describing past and present medical efforts to treat OGD.

RESULTS

The consistent theme throughout the existing medical literature is that no standard treatments exist for dysosmia or dysgeusia, including for drug-induced chemosensory dysfunction. According to Henkin, drugs in every major pharmacological category commonly impair both taste and smell function.² Schiffman aptly states that this is due to the unique biological effects of each drug.³ To further complicate the matter, regardless of the causative mechanism, OGD treatment is vastly unconsidered and underdeveloped. Vent et al stated that pharmacology can't reliably achieve recovery of olfactory function after viral infection.⁴

Investigation of multiple pathways resulting in OGD due to COVID-19 would be appropriate, including examination of any concomitant effects of medications that any patient may currently be taking before and after COVID-19 infection. Research for this review revealed a surprisingly sparce body of work regarding OGD treatment.

Most studies have been small, have had vague findings and conclusions, and have made fairly weak recommendations. For example, Boesvelt et al's 2017 clinical review on anosmia concluded that limited evidence-based treatments existed for anosmia.⁵ In part 3 of this review, the author will discuss his treatment approach based on clinical success and considering the information found in this review of the medical literature. This review of current approaches serves as prerequisite background.

Current Approaches

Natural spontaneous resolution. Testimony to the insufficient research attention paid to OGD over decades is the fact that despite its long-known existence as a medical phenomenon, it's only now during a global crisis that medical practitioners are taking it seriously. Data from Duncan and Seiden's 1995 study, which considered long-term olfactory effects from both head trauma and upper respiratory tract infection, suggested that improvement can take place but could take several years.⁶ Obviously, due to the recent emergence of COVID-19 related OGD, medical practitioners don't know if natural resolution will occur in chronic cases, or how long it might take.

In 2006, Welge-Lussen and Wolfensberger studied olfactory disorders from postviral upper respiratory tract infections.⁷ They indicated that spontaneous recovery might occur within 2 years, but no proven effective therapy existed at the time. They thought that olfactory training (OT) might be promising.

Throughout a preponderance of nonacademic Internet sources, no shortage of opinions exist from physicians and the lay public. The watch-and-wait approach for post-COVID-19 patients to regain their normal olfactory and gustatory function appears ambiguous, inconsistent, and risky, particularly with an unknown entity, a novel coronavirus.

The focus of study is justifiably more pertinent to individuals with persistent chronic PCOGD. However, like many maladies, early intervention could be the most effective, to prevent resolution from becoming implausible or extremely arduous by waiting for chronic dysfunction to manifest.

Olfactory training. Numerous articles and reviews before and after COVID-19 have espoused OT, also known as scent training (ST), as the primary recommendation for treatment of OGD to date. For example, Duyan et al succinctly stated that physicians should refer a patient to an otolaryngologist for scent training if parosmia is detected.⁸

Choi et al reported a 40% improvement from OT with 104 patients in Korea.⁹ Koyama et al performed a comprehensive and detailed review of phytochemicals to be considered for PCOGD olfactory training. Those authors studied the biochemistry, anti-inflammatory potential, and antiviral effects of various plant-derived essential oils in great depth, as potential supports for OGD.¹⁰

A plethora of studies and reviews have reiterated the rationale for OT as the most appropriate currently investigated therapeutic measure for PCOGD. Al Ain et al declared that improvement from intensive OT was associated with changes that may be related to modifications occurring directly in the brain.¹¹

Dicpinigaitis contended that OT is the only approach with significant scientific support; sufficient investigation of

pharmacological measures hasn't occurred in clinical trials. Of significance is Dicpinigaitis' opinion that an opportunity has arisen for physicians outside of the otorhinolaryngological field to become familiar with postviral olfactory dysfunction and OT.¹²

Corticosteroids (CS). The globally relevant association between coronavirus disease 2019 and olfactory dysfunction has sparked an unprecedented demand for treatment. Medical practitioners have considered systemic corticosteroids as a therapeutic measure. However, long-term evidence and medical consensus is understandably unclear as to whether CS treatment for PCOGD is or isn't safe and appropriate.

Yuan et al's 2021 systematic review in *Frontiers in Neuroscience* discusses their analysis of 273 abstracts and 20 articles with data from 2415 patients.¹³ They concluded that a combination of OT and direct administration of steroids in the olfactory cleft was promising.

Le Bon et al's pilot study supported that treatment's safety, in conjunction with OT.¹⁴ Genetzaki et al contended that the percentage of improvement through methylprednisolone treatment was insufficient to suggest it as a first-line treatment.¹⁵ They reported that the evidence was weak for its value as a treatment for postinfectious olfactory dysfunction.

It's undisputed and well established medically that oral and intravenous CS can impair immune-system function. Huart et al's large group of researchers reported in the 2021 International Forum of Allergy & Rhinology about the need for caution in the use of systemic CS.¹⁶ These researchers from the University of East Anglia insisted that physicians shouldn't use CS for anosmia due to COVID-19. They based their opinion upon a lack of supportive evidence, a high rate of spontaneous recovery, and sufficient and well-known evidence of potential adverse effects. While that group of experts encouraged randomized placebo-controlled trials, they emphasized the use of OT as the initially considered treatment, involving inhalation of at least four odors, twice daily for several months. They based this recommendation on much greater evidence for the benefits of OT than for CS and on OT's lack of side effects.

Additionally, Whitcroft and Hummel's 2019 review in *JAMA Otolaryngology - Head & Neck Surgery* on management of olfactory dysfunction didn't support the use of oral and intranasal CS due to a lack of evidence and the potential for harm.¹⁷

The Cochrane Library is a collection of databases of high-quality, independent evidence to inform healthcare decision making. Webster et al's 2021 article in the Cochrane Database of Systematic Reviews asserted that evidence in support of intranasal CS, from a study of 100 participants, was of very low certainty regarding both benefit and harm.¹⁸

Researchers posted a clinical trial at ClinicalTrials.gov in August 2020 that evaluated the effects of CS on OGD related to community-acquired pneumonia.¹⁹ Other researchers posted a French trial that evaluated the efficacy of the steroid budesonide in April 2020.²⁰ Its results weren't available at the time of this article. Physicians can construe the uncertainty of whether steroid treatment can or can't impair the recovery of those actively infected with COVID-19 as sufficient evidence for exhibiting caution in its prescription for OGD. It's obvious that physicians shouldn't discontinue essential, life-supportive, steroidal medications. However, physicians and patients alike may exhibit legitimate concern with any attempts to treat nonlife-threatening OGD with any agent capable of increasing their risk for infection. The need for nonpharmacological approaches to treating the olfactory and gustatory sequalae of COVID-19 and other infections is clear.

Combination of OT and CS. Le Bon et al's 2021 pilot study investigated the safety and effectiveness of a combination of CS and OT for post-COVID-19 anosmia. The researchers cited that fewer side effects occurred compared to those with CS alone and that positive results warranted larger studies.¹⁴ Members of the Clinical Olfactory Working Group professed an overwhelming recommendation for OT. ²¹ They couldn't make the same case for oral steroids. They derived their conclusions from analysis and review of 107 articles and asserted the need for further research for other therapeutic options.

Omega-3 supplements. Evidence that supports the use of omega-3-fatty-acid supplementation for OGD is weak at best. The Icahn School of Medicine at Mount Sinai posted a clinical trial in August of 2020, *COVID-19 Anosmia Study*, at ClinicalTrials.gov.²² It was a randomized, double-blind, placebo-controlled study intended to evaluate both objective and subjective perception of olfactory dysfunction over a period of 6 weeks after infection.

Omega-3-fatty-acid supplements are available over the counter; however, as for any supplements, individuals should exhibit caution due to possible drug interactions. Omega-3 fatty acids are richly present in various natural foods, including various types of fish, seeds, and nuts. To a lesser extent, they are bioavailable in eggs, meats, and various dark green plants.

Because this nutrient is fairly omnipresent, isolating it as a specific and sole treatment variable has its challenges. No evidence exists of any data collected or any means existing to determine if a deficiency of omega-3 in the diet predisposes individuals to OGD. However, it would seem rational for persons afflicted with it to increase consumption of the aforementioned foods and for physicians to recommend that increase.

Zinc supplementation. A 1998 study in *Cancer* reported the effectiveness of zinc supplementation for cancer patients suffering taste abnormalities after radiation treatment.²³ Najafizade et al's 2013 study concurred, concluding that supplementation can prevent radiation-induced taste alterations.²⁴

It's uncertain whether the coronavirus itself is causative for COVID-19 patients exhibiting zinc deficiency or not. Al-Awfi's 2020 study found that 57.4% of COVID-19 patients had a zinc deficiency. However, the researchers concluded that evidence and means for further research were insufficient to indicate if the virus was causative, coincidental, or present prior to infection. $^{\rm 25}$

Halyard et al in 2007 concluded that zinc sulfate, as prescribed in their trial, didn't prevent taste alterations in cancer patients receiving radiation therapy.²⁶ Kumbargere et al's 2017 study reported very low-quality evidence to support zinc supplementation's effectiveness in improving taste acuity as well as in improving health-related quality of life.²⁷ Khan et al's 2019 double-blind, randomized controlled trial supported the conclusion that zinc sulfate wasn't beneficial in preventing chemoradiation-induced taste and smell alterations.²⁸

It's also evident that excessive or inappropriate use of supplemental zinc isn't without risks. Jafek et al in 2004 reported cases of severe hyposmia and parosmia that intranasal zinc-gluconate treatment induced. Those researchers stated that zinc ions are toxic to the olfactory epithelium, which isn't a natural route for introduction of the essential mineral to the body.²⁹ In 2006, Alexander and Davidson documented intranasal zinc as a causative agent for anosmia in 17 cases.³⁰

Perhaps the world's population should become focused on improving dietary zinc intake, where applicable. If zinc indeed has a therapeutic value toward combating postviral OGD, its inclusion as preventative healthcare should be an obvious pursuit for all. Its value as a post-radiotherapy measure for cancer patients fortifies that assertion. However, zinc supplementation's classification as a pharmacological therapy might detract from promoting healthier eating; zinc is a mineral nutrient present in a wide variety of whole natural foods.

Turmeric. Turmeric is tremendously touted as a wonder supplement due to its curcumin content. While fairly substantial evidence supports its various benefits, most of the available public knowledge may not come from that evidence. Turmeric is massively marketed as a miraculous, natural, anti-inflammatory agent, in particular for those seeking nonpharmaceutical aid.

Gupta et al's 2013 review on the therapeutic roles of curcumin determined in clinical trials certainly reveals its potential for managing various human diseases.³¹ In pursuit of furthering the study of turmeric, Chabot and Huntwork reported two cases of PCOGD resolved through a single 1000-mg ingestion of turmeric extract.

Participant one was a 25-year-old man whose OGD persisted for 45 days. Participant two had symptoms for only 4 days before taking the supplement. The researchers indicated that the risk of a single dose of turmeric, for those not on medications metabolized by cytochromes p450, was low and the potential benefit high.³² These cases, however, in no manner demonstrate the potential for turmeric for severe and chronic cases, such as those experiencing OGD for more than a year after COVID-19.

Although the public seems to assume that safety is inherent for products promoted under the banner of natural, consumers must use concentrated substances derived from plants with knowledge and caution. Unlike the consumption of natural whole foods rich in zinc and omega-3 fatty acids, turmeric supplementation shouldn't occur indiscriminately or be taken in excessive dosages and frequency. Nevertheless, it appears that its judicious usage for PCOGD is worth considering.

Alpha-lipoic acid. Hummel et al investigated the potential therapeutic benefits of the antioxidant alpha-lipoic acid for olfactory loss after upper respiratory infection.³³ They considered its mechanisms, including the release of nerve growth factor and antioxidative effects intended to support regeneration of olfactory receptor neurons. In their 23-patient study, the researchers concluded that the nutrient may be helpful, justifying double-blind, placebo-controlled studies of larger cohorts.

Some healthcare providers frown upon supplementation due to its potential dangers, particularly when issues seem likely for those desperate for anything that might restore normal taste-and-smell sensations. Consumption of sufficient quantities of whole foods that contain the beneficial substances is quite arguably, safer.

Hadzik et al reported a cautionary tale about nutrient supplements not always being harmless in their 2014 case report of an intentional fatal overdose of alpha-lipoic acid for an adolescent girl.³⁴ As this review similarly did in its evaluation of the benefits of zinc and omega-3 fatty acids, its evaluation of the naturally-occurring nutrient, alpha-lipoic acid indicates caution in the use of a supplement that is present in a wide variety of whole foods from both plant and animal sources.

Current Clinical Trials

To date, a smattering of clinical trials have investigated the prospect of support for PCOGD.

Cerebrolysin. Hamed hypothesized that Cerebrolysin—a medication primarily administered for the effects of ischemic and hemorrhagic stroke, traumatic brain injuries, dementia, and cognitive decline—might have benefits for post-COVID-19 anosmia and ageusia.³⁵ The researcher suggested that the neurotrophic polypeptides in this medication may be supportive of the promotion of recovery from neurodegenerative and acquired nervous-system diseases.

Intranasal theophylline. Pharmacologists have described theophylline as having a very narrow therapeutic window, with limitations on its use due to drug interactions. It also requires extreme caution in older patients because of an increased risk of serious toxicity.³⁶

Henkin et al's 2012 study evaluated and compared oral and intranasal theophylline in a 10-patient cohort.³⁷ The researchers concluded that intranasal treatment was safer and more effective than oral administration, with no adverse effects being reported.

At the time of this review, researchers have organized a phase II, single-site, double-blinded, placebo-controlled randomized clinical trial. They are recruiting participants to evaluate the safety and efficacy of intranasal theophylline for PCOGD as a possible treatment for COVID-19-related olfactory dysfunction. This medication is a known phosphodiesterase inhibitor for the treatment of asthma.

Theophylline has shown benefits in similar clinical trials for postviral olfactory dysfunction.³⁸ Ahmed posted another clinical trial on Clinicaltrials.gov on November 3, 2021 that intended to evaluate 75 participants' responses to the treatment combination of intranasal insulin, zinc, gabapentin, and ice-cube stimulation for PCOGD.³⁹ The expected end date is June 2023.

DISCUSSION

This review has presented an overview of the current state of knowledge on the pathophysiology of and treatments for OGD, as triggered by the infection of COVID-19. It appears that while most COVID-19-related cases of smell and taste dysfunction have naturally resolved, chronic cases are widely prevalent.

It's unambiguously evident that disturbances to both taste and smell have been common historically, but physicians have poorly considered or expressed concern about them in clinical medical practice. The author's review of medical literature reveals very limited evidence of pre-COVID attention. OGD is a consequence of conditions such as COVID-19, rather than a distinct diagnosed malady. It's abundantly clear that OGD patients' symptoms are ones that medicine at large has never faced with such an ominous onslaught, as per its emergence as a major symptom of COVID-19.

Sometimes it takes an emergency to arouse attention for a long existing problem that medical practitioners should always have taken more seriously. Practitioners of many medical disciplines have notoriously taken OGD patients for granted prior to the pandemic. An overview of this situation compels one to draw the conclusion that physicians have perceived losing the sense of smell or taste as a minor malady, perhaps compared to becoming deaf or blind.

Extremely limited evidence-based treatment has existed for OGD precipitated by any known cause. Global demand for any treatment capable of reducing or resolving gustatory and olfactory disorders triggered by COVID-19 is unprecedented. Past and present treatment approaches and recently initiated clinical trials, since the onset of the pandemic, have yet to yield any significant results.

The majority of such investigations have focused on the potential for new applications of existing medications and other modalities. Treatment approaches that researchers have already investigated for safety and effectiveness for other disorders might be well-suited for consideration for the current quandary of the urgent taste-and-smell-dysfunction dilemma. Thus, with the dismal dearth of medical support for a suddenly prevalent, but hardly novel, set of maladies, the imperative for multifaceted and broad investigations across all medical disciplines is without question.

The history of the diagnosis, scientific investigation into mechanisms, and treatment of these sensory disorders has

been, at best, unremarkable and insufficient. Might this be because a loss or distortion in taste or smell is hardly lifethreatening? Is it possible that its diminishing effects on one's quality of life requires an empathetic fellow sufferer to appreciate its significance? Is it, at least in part, due to the fact that no specific or consistent treatments have existed? Should it be unsurprising that it's more convenient to ignore the symptoms when no treatment is available? Terms such as anosmia, ageusia, dysosmia, and phantogeusia, are becoming known to the lay public, accompanied by the appropriate demand for medical solutions.

An abundance of medical literature exists that repetitively reinforces the consensus that viral infections can trigger OGD and that the pathogenesis for sensorineural deficits is both poorly studied and uncertain. Most important, it appears universally agreed that OGD has been, and still is, extremely challenging to treat.

It's not the intention of this review to further harp upon this international consensus. Inarguably, furthering the knowledge of the pathophysiology and mechanisms of post-COVID-19 OGD could pave the way for development of effective treatments that address neurological impairments. The demand for them is crystal clear. It's hopeful that response can manifest from innovative applications of existing therapies, medications, nutritional measures, and other modalities, as well as new perspectives, paradigms, procedures, and products.

CONCLUSIONS

Physicians have given disorders of taste and smell sensation only a modicum of medical mention until the sudden demand due to COVID-19-associated symptoms. Evidence that any specific treatment holds promise for promoting the restoration of olfactory or gustatory function is extremely limited. Part 3 of this review will address the potential of auricular cranial nerve stimulation, focusing on a natural resolution.

AUTHOR'S DISCLOSURE STATEMENT

The author declares that he has no conflicts of interest related to the study.

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