



# Novel Therapies in Olfactory Disorders

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## Abstract

**Purpose of Review** To summarize and critically review the recent literature on novel treatments for olfactory disorders (OD). **Recent Findings** Emerging therapies in the management of OD include multiple vitamins and supplements, biologics, neuromodulators, and intranasal agents. There is also an active investigation into treatments that harness the neuroregenerative properties of the olfactory epithelium, such as platelet-rich plasma and stem cell transplantation. **Summary** Successful management of OD is multimodal and tailored to the underlying etiology. As the findings of further investigations accrue, the management of OD will undoubtedly continue to be advanced and refined, and likely harness the intrinsic neuroregenerative properties of the olfactory system.

**Keywords** Olfaction · Olfactory loss · Olfactory dysfunction · Olfactory disorders · Smell loss

## Introduction

The frontiers in treatment for olfactory dysfunction (OD) are as broad and exciting now as they have ever been. While advances in the treatment of olfactory disorders have been building over the last few decades, the COVID-19 pandemic has bolstered a new wave of interest in the treatment of smell dysfunction among not only the scientific community but also the public zeitgeist worldwide. As a result, there has been a surge in recent data regarding new treatments for olfactory disorders that can serve to augment the established pillars of olfactory training and intranasal corticosteroids [1•, 2–5]. Here we discuss several emerging therapeutics for olfactory disorders.

## Biological Agents

In chronic rhinosinusitis with nasal polyps (CRSwNP), inflammatory mediators acting at the olfactory epithelium have been implicated in the olfactory loss. In CRSwNP, interleukin (IL)-5

is present at elevated levels within the mucus of the olfactory cleft, and IL-5 levels are significantly associated with the severity of OD [6]. With the increasing role of biologics that target these inflammatory mediators in the management of CRSwNP, evidence of their efficacy in managing olfactory loss related to CRSwNP is also increasing.

Dupilumab, a monoclonal antibody against IL-4 and IL-13, has been demonstrated in RCT-level data to have significant improvement in UPSIT scores at 12, 24, and 52 weeks compared with placebo in patients with CRSwNP [7, 8]. Omalizumab, a monoclonal antibody against IgE, also demonstrates significant improvement in UPSIT scores at weeks 8 and 24 when compared with a placebo [9]. Interestingly, mepolizumab, a monoclonal antibody against IL-5, has not been shown to have significant improvement in olfactory outcomes compared with placebo, despite improving other clinical endpoints for CRS [10, 11]. Biologics may be an important tool in the near future in the management of CRS-related OD, with further study needed to better refine indications and patient selection.

## Vitamins and Supplements

Numerous vitamins and supplements have been investigated in the management of OD and may represent important, accessible treatment adjuncts that assist the neuroregenerative properties of the olfactory epithelium. It should be noted; however, that the existing studies are of varying quality and quite heterogeneous in nature.

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### Omega-3

Omega-3 fatty acids play an important role in lipid metabolism and have additional anti-inflammatory and antioxidant properties. Omega-3 supplements have been shown to have neuroprotective effects in diseases such as Alzheimer's disease or diabetic neuropathy [12, 13], and in rat models have been shown to improve performance in olfactory-cued tasks [14].

An Australian population study found that older adults with a high consumption of omega-3 fatty acids in their diet had lower odds of OD [15]. The benefit of omega-3 supplementation has also been investigated in the post-surgical setting in a recent double-blinded–placebo-controlled RCT [16]. Following endoscopic skull base surgery, patients that took omega-3 (1000 mg twice daily) experienced significantly higher UPSIT scores at 3 months and 6 months post-operatively [16]. While promising, additional studies are warranted to investigate the role of omega-3 in OD outside of the postsurgical setting.

### Vitamin A

Vitamin A is thought to play a role in the regeneration of olfactory receptor neurons, yet its role in the treatment of OD is currently questionable, with the need for higher-quality studies. Intranasal vitamin A with OT has been shown in a retrospective study to improve olfactory discrimination for all etiologies of OD, with the greatest improvements seen in the post-infectious OD group [17]. There is currently a double-blinded–placebo-controlled trial underway investigating the efficacy of intranasal drops of vitamin A for post-viral olfactory loss, which will assess both olfactory outcomes as well as volumetric change in the olfactory bulb on MRI [18].

Systemic vitamin A has not been shown to have benefit, as a double-blinded–placebo-controlled RCT found that vitamin A (10,000 ug daily for 12 weeks) did not demonstrate any improvement in olfactory scores [19].

### Zinc

Zinc is an essential element for enzymes that participate in cell division and proliferation and may have a potential role in the maintenance of the olfactory epithelium. Specifically, in the setting of post-traumatic anosmia, oral zinc gluconate (10 mg three times per day) has been shown to have improvements in olfactory threshold testing [20]. However, in a study of post-chemotherapy OD, oral zinc had no benefit and even a trend toward worsening in the zinc group compared to placebo [21]. Similar to vitamin A, perhaps more study is needed before establishing the

use of zinc for other etiologies of OD. Clinicians considering oral zinc supplementation for OD should be aware of the potential adverse effects, including gastric distress, neutropenia, and iron deficiency anemia. It should be noted that intranasal zinc is recommended *against* for the treatment of OD, as it has been shown to have potentially irreversible damage to olfaction function [1••, 22].

### Toki-shakuyaku-san (TSS)

TSS is a Japanese herbal medicine with anti-inflammatory and immunomodulatory properties used to treat a multitude of diseases across the gynecological, gastrointestinal, and neurological systems. There is low-level evidence in the form of retrospective case serieses to suggest that oral TSS can also improve olfactory recovery in post-infectious OD, with reported rates of recovery ranging from 43–77% [23, 24]. Prospective, controlled studies are needed to better evaluate the efficacy of TSS in the management of OD.

### Sodium Citrate

Free calcium in the olfactory epithelium may act to inhibit the processing of olfactory signals; therefore, it is thought that the introduction of a buffering solution such as sodium citrate to reduce free calcium may improve OD. Intranasal delivery of sodium citrate has shown early promise in the management of OD, particularly in the post-infectious setting, as two prospective trials showed improvements, albeit temporary, in olfactory outcomes following the administration of sodium citrate [25, 26]. In a study of 55 patients comparing 9% sodium citrate intranasal spray to sterile water, sodium citrate demonstrated significant improvement in olfactory threshold lasting up to 120 min after application, and the treatment response rate was 33% compared to 0% in the control group [26]. It should be noted that existing studies demonstrate olfactory benefit in the relatively short term following sodium citrate administration (on the magnitude of minutes to hours), and that it does not appear useful in terms of permanent or long-term efficacy. However, sodium citrate may still provide a useful therapy for patients in the time period when they are preparing to eat and enjoy their food and drink.

### Insulin

Insulin receptors are present throughout the central nervous system, including the olfactory bulb, though their specific function in olfaction is not well understood. There

is some data to suggest that intranasal insulin may have a benefit in improving olfactory threshold. A pilot study found of 10 patients with post-infectious OD found a very small threshold improvement in 60% of patients [27]. In a placebo-controlled RCT of 36 patients with undifferentiated OD (18 in each treatment arm), patients underwent olfactory cleft placement of gel foam soaked with insulin versus placebo twice weekly for 4 weeks; intranasal insulin demonstrated a very slight improvement in the olfactory threshold, without significantly changing serum insulin or glucose levels [28].

## Neuromodulators

There is very little evidence regarding the management of parosmia/phantosmia, with the majority of existing studies as level 3 or level 4 evidence [29•]. However, there is an urgent and increasing need for treatments with the rise of parosmia/phantosmia associated with COVID-19 [30]. Neuromodulating agents with antipsychotic, antiseizure, and/or antimigranous properties such as haloperidol, topiramate, verapamil, gabapentin, and nortriptyline may have some benefit in preliminary studies assessing parosmia/phantosmia [29•, 31, 32]. Preliminary data also suggests that gabapentin may improve COVID-19 related parosmia, where 5 of 9 patients experienced significant improvements in UPSIT scores [33]. It should be noted; however, that 2 of these 9 patients had to discontinue gabapentin due to adverse effects. Given the potentially significant side effects of these neuromodulating agents, the further rigorous study is certainly needed to evaluate their risk and benefit, and close monitoring of patients prescribed these medications is warranted.

## Platelet Rich Plasma

Platelet-rich plasma (PRP) is an autologous blood product that has both anti-inflammatory and pro-regenerative properties, used in many inflammatory and neuropathic conditions. In anosmic mouse models, topical application of PRP in the olfactory cleft induced significantly more growth in olfactory epithelium thickness and exhibited less epithelial damage compared to saline application [34]. There have been two pilot single-arm studies investigating the efficacy of intranasal PRP for OD in humans, and although relatively small, these early studies are promising. In a study of 5 patients where PRP was injected into the olfactory groove 4 times over the course of 7 months, 4 patients recovered subjective olfaction and had a mean improvement from a pretreatment score of 0.19–4.92 out of 10 [35]. Another study of 7 patients performed a single injection

of PRP and found significant improvements in TDI score in patients starting with hyposmia ( $16 < \text{TDI} < 30$ ), while those starting with anosmia ( $\text{TDI} < 16$ ) did not have significant improvement [36•]. A recent randomized placebo-controlled trial demonstrated that PRP injections into the olfactory cleft can have significant improvements in olfactory threshold and discrimination for COVID-19-related olfactory loss [37]. In this RCT of 26 patients, 8 of 14 (57.1%) patients treated with PRP achieved clinically meaningful improvement ( $\Delta > 5.5$  points) in Sniffin' Sticks testing compared to 1 of 12 (8.3%) placebo subjects (adjusted odds ratio 19.2, 95% CI 1.3–291,  $p = 0.03$ ), without any adverse effects noted.

## Electrostimulation

Electrical stimulation therapy represents another novel area of exploration in the treatment of OD, as it has been shown to help nerve regeneration in other conditions such as traumatic brain injury and peripheral neuropathy [38, 39]. In a pilot study of 5 patients with OD following endoscopic sinus surgery, electrical stimulation delivered through electrodes positioned at the lateral lamella of the cribriform induced subjective smell perception in 3 patients [40•]. The senior author (ZMP) is also carrying out translational studies evaluating electrical stimulation to the olfactory system via other mechanisms. While additional more rigorous studies are needed to validate and correlate subjective smell perception with objective electrophysiologic findings, the results of these studies suggest that electrostimulation may be a potential treatment option for OD in the future.

## Stem Cell Therapy

The olfactory epithelium is uniquely one of the few sites of the human body where neurogenesis continues into adulthood. This is thought to be mediated by two populations of stem cells: globose basal cells (GBCs), which actively replace cells in the olfactory epithelium, and horizontal basal cells (HBCs), which are dormant cells whose differentiation into GBCs is activated following acute epithelial injury [41]. There is an early but promising investigation being performed in harnessing the regenerative properties of these stem cells in the olfactory epithelium for the treatment of OD. GBCs have been successfully cultured [42, 43], and recently, the ability to culture HBCs from the human olfactory epithelium has been established [44•]. This has given investigators the opportunity to better understand molecular mechanisms driving multipotency as well as the ability to test stem cell potency via

transplantation. In mouse models of anosmia induced by olfactotoxic gas methyl bromide, HBCs transplantation yielded multiple cell types in the olfactory epithelium, including neuronal cells with apical processes and sustentacular cells, demonstrating that the multipotency of stem cells can be maintained through transplantation [44•]. An additional mouse study found that intranasal delivery of GBCs via intranasal drops induced new olfactory neuron formation in the olfactory bulb and restored food-smelling behaviors [45]. Further validation in animal models is needed, and no testing of olfactory progenitors has been performed yet in humans. Nonetheless, therapeutic strategies that harness the unique regenerative property of the olfactory system may be promising avenues in the future of olfactory loss treatment.

## Conclusions

OD is complex in nature, as there are multiple etiologies, clinical manifestations, and varying prognoses to treatments. In general, successful management of OD is multimodal and tailored to the underlying etiology and clinical nature of the OD. While olfactory training and intranasal corticosteroids serve as the foundational regimen in the management of OD, there may be opportunities to improve benefit in through the emerging therapies discussed here. Future potential avenues in the management of OD will likely harness the neuroregenerative properties of the olfactory system. While meaningful progress has been made in understanding OD over the last 2 decades, there remains a tremendous amount to learn and refine in the treatment of OD. Knowledge in the management of OD will undoubtedly continue to accelerate with more intriguing discoveries in the coming years.

## Declarations

**Conflict of Interest** Michael T. Chang declares that he has no conflict of interest. Zara M. Patel reports royalties or licenses from Springer and Wolters Kluwer; consulting fees from Medtronic, Wyndly, Dianosic, Ethicon/Johnson & Johnson, Mediflix, and Consumer Medical; patent pending (S15-465 63/076,656 [S31-06935.PRO]); participation on a Data Safety Monitoring Board or Advisory Board for Optinose and Regeneron/Sanofi; and stock or stock options for Olfera Therapeutics.

**Human and Animal Rights and Informed Consent** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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  - Of major importance
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