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REVIEW ARTICLE

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Clinical studies in COVID-related olfactory disorders: Review of an institutional experience

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Abstract

Objective: To share a single institutional experience with clinical research on COVID-related olfactory dysfunction (OD).

Data Source/Method: Narrative review of published original data and ongoing clinical trials on COVID-related OD at Washington University from 2020 to 2023.

Results: There were three new diagnostic-/patient-reported outcome measures developed and tested. We report five clinical trials of interventions for COVID-related olfactory disorders: combined Visual-Olfactory Training (VOLT) with patient-preferred scents versus standard olfactory training (*VOLT trial*), oral gabapentin versus placebo (*Gabapentin for the Relief of Acquired Chemosensory Experience trial*), nasal theophylline irrigations versus placebo (*Smell Changes and Efficacy of Nasal Theophylline trial*), stellate ganglion block (single-arm), and mindfulness-based stress reduction (MBSR) versus lifestyle intervention *(MBSR trial)*.

Conclusions: Initial intervention trials for COVID-related OD have shown potential for improving subjective and objective olfactory outcomes. However, there remains no gold standard treatment that definitively outperforms placebo in controlled trials. Therefore, continued investigation of novel therapeutic strategies for COVID-related OD is necessary to maximize olfactory outcomes for affected patients.

KEYWORDS

chemosensory disorders, COVID, olfactory dysfunction

Key points

There are several potential interventions for COVID-related olfactory disorders, however, more evidence is needed to establish the most effective treatment strategies for olfactory outcomes.

INTRODUCTION

Infection with SARS-CoV-2 is a leading cause of olfactory dysfunction (OD) worldwide, affecting millions of people over the last 3 years. While many return to normal smell within weeks after initial infection, recent meta-analyses suggest that OD persists beyond 6 months in 5%–30% of patients.[1,2] Among patients presenting with smell loss concerns at Washington University in St. Louis, the rate of persistent subjective OD is approximately 30% at 2 months and 20% at 6 months after COVID diagnosis with olfactory symptoms during

presentation.[3] Rates of objective smell loss on smell identification testing are even higher, with 75% of patients having abnormal scores at 2 months and 55% at 6 months. Numerous strategies have been tested in different populations to manage COVID-related OD, however, few treatments have proven effective.[4] The best choice of clinical outcome for OD trials is also uncertain due to the incongruence of chemosensory results with patient symptoms.

We report several recent and ongoing studies in the COVID-19 population including Visual-olfactory Training (VOLT), nasal theophylline irrigations, gabapentin, stellate ganglion block, and mindfulness-based stress reduction (MBSR). We report the development of three new diagnostic and patient-reported outcome measures (PROM) which are used in these trials.

OUTCOME MEASURE DEVELOPMENT

Clinical Global Impressions (CGI) scales

Several of the discussed studies use an adapted CGI scale as a primary outcome.[5] In the CGI for Severity (CGI-S), participants answer the question, "Overall, what is your current ability to smell?" with six response options (absent, poor, fair, good, very good, or excellent). In the CGI for Improvement (CGI-I) for smell, subjects rate their change in smell after the study intervention on a 7-point Likert scale (1—*much better*, 2—*somewhat better*, 3—*slightly better*, 4—*neither better nor worse*, 5—*slightly worse*, 6-*somewhat worse*, and 7—*much worse*). The question is phrased to capture the perceived change in the sense of smell attributed to intervention, for example, "Compared to your sense of smell before you started nasal irrigations, how would you rate your sense of smell now?" Patients are classified as responders if they report at least slightly better smell. A minimal clinically important difference (MCID) in response rate between study arms is set at 25% because this corresponds to the number needed to treat of four which was deemed reasonable by investigator consensus.

Novel anosmia screening at leisure (NASAL)[6]

This study aimed to develop and validate a cost-effective and easily administered chemosensory screening test for OD of any etiology. We recruited 115 adults with self-reported impaired smell related to COVID, excluding pregnant women and those with initial COVID or other viral infection symptoms in the last 4 weeks. Participants rated 45 household items as (0) cannot smell, (1) smells less strong/different than normal, and (2) smells normal. These were reduced based on content validity to seven items with seven alternatives spanning different clusters of smell descriptors: soap (or tea leaves), burnt candle (or cinnamon), peanut butter (or honey), herbs such as rosemary, thyme, basil (or spice such as tarragon, turmeric, paprika), garlic (or seasoning for meat), lemon (or citrus fruit additive), and coffee (or chocolate). The highest possible score is 14, with score categories of anosmia (0–4), severe dysfunction (5–7), mild dysfunction (8–10), and normosmia (11–14). Items were further reduced to create the NASAL-3, in which subjects smell just soap, burnt candle, and coffee or their alternatives.

The NASAL-7 and NASAL-3 were validated against the University of Pennsylvania Smell Identification Test (UPSIT). In the UPSIT, scores out of 40 correspond to categories of OD including normosmia (≥34 in males, ≥35 in females), mild hyposmia (30–33 in males, 31–34 in females), moderate hyposmia (26–29 in males, 26–30 in females), severe hyposmia (19–25), anosmia (6–18), and malingering (≤5). A cutoff of 7/14 on the NASAL-7 was optimal for classifying patients as having at least moderate hyposmia on UPSIT versus not, with 79% sensitivity (95% confidence interval [CI]: 66%–89%), 70% specificity (95% CI: 58%–80%), and area under the receiver operating characteristic curve [AUC] 0.814 (95% CI: 0.727–0.900). A cutoff of 2/6 on the NASAL-3 had 57% sensitivity (95% CI: 36%–76%), 78% specificity (95% CI: 69%–85%), and AUC 0.658 (95% CI: 0.503–0.814) to discriminate between participants with vs without anosmia on UPSIT. There was moderate agreement between UPSIT-defined OD categories and those defined by NASAL-7 (weighted $\kappa = 0.496$; 95% CI: 0.343–0.649) and those defined by NASAL-3 (weighted $\kappa = 0.365$; 95% CI: 0.187–0.543). Patients at home or healthcare workers may use this brief and inexpensive diagnostic tool, particularly if other chemosensory tests are unavailable.

Olfactory dysfunction outcomes rating (ODOR)[7]

This study aimed to develop and validate an olfaction-specific quality-of-life PROM to capture the physical problems, functional limitations, and emotional consequences of OD. Items were developed using online narratives of 1000 patients with OD, 30 patient interviews, and review by four otolaryngologists. Data on the etiology of OD were not collected. The instrument was reduced to 28 items with each item scored as (0) no difficulty/very rarely bothered to (4) very frequently bothered. The total score range was 0–112, with higher scores indicating more severe OD.

Survey validation was performed with 283 patients with COVID-related OD enrolled in six other studies that used ODOR as a secondary outcome measure, including the NASAL, VOLT, Smell Changes and Efficacy of Nasal Theophylline (SCENT), and SCENT2 trials.[6,8–10] The instrument had high internal consistency (Cronbach $\alpha = 0.968$), test–retest reliability ($r = 0.90$ [95% CI: 0.81–0.95]), face validity, content validity, concurrent validity ($r = 0.87$ [95% CI: 0.80–0.91] compared with the Questionnaire of Olfactory Disorders-Negative Statements; $\rho = -0.76$ [95% CI: −0.81 to −0.71] compared with a patient-reported symptom severity scale), and divergent validity (mean score difference: −33.9 [95% CI: −38.3 to −29.6] between normosmic patients and hyposmic/anosmic patients). The MCID was 15 points.

Parosmia Olfactory Dysfunction Outcomes Rating (DisODOR)[11]

In addition to loss of smell (anosmia/hyposmia), dysosmias such as smell distortions in the presence (parosmia) or absence (phantosmia) of an odorant are recognized presentations of COVID-related OD.[4] Current PROMs do not substantially address dysosmia-related quality-of-life, therefore, this study aimed to develop and validate a PROM for parosmia. Items were developed using secondary analysis of experiences reported in an online support group of 9000 users with COVID-related smell and taste disorders. Four otolaryngologists narrowed the items to a 59-question pilot survey. This was tested in 134 patients with COVID-related OD persisting for ≥3 months and 20 controls. The items were reduced to 29 questions and the otolaryngologists determined that all items met face and content validity. The score range was 0 to 116, with higher scores indicating more severe OD.

The mean score difference between cases and controls was 45.0 (95% CI: 40.5–49.5) displaying good discriminative validity. *DisODOR* had strong test-retest reliability ($r = 0.942$) with high internal consistency (Cronbach's $\alpha = 0.971$). *DisODOR* had moderate correlation with *Sino-Nasal Outcomes Test*-22 scores ($r = 0.619$) indicating good convergent validity. There was excellent association with CGI-S categories ($\eta^2 = 0.447$). The MCID was 15 points based on distribution.

Clinical trials

Clinical trials at Washington University specifically addressing COVID-related OD are summarized in Table 1. A detailed discussion of each study follows.

Combined VOLT with patient-preferred scents[8]

Olfactory training (OT) is a treatment used to stimulate olfactory recovery in postviral OD (PVOD). However, studies of OT have had variable duration, odor concentrations, and supplemental pharmacological interventions, and the efficacy of OT in COVID remains unproven. Dual-sensory (olfactory and visual) stimulation may potentiate olfactory neuroplasticity via cross-modal sensory transfer and improve adherence to OT protocols. In this randomized, 2 × 2 factorial trial, patients underwent bimodal training with patient-preferred scents, bimodal training with physician-assigned scents, unimodal training with patient-preferred scents, unimodal training with physician-assigned scents, or no training. After enrollment of the required sample size, additional eligible individuals were invited to participate in a control group and were instructed not to conduct OT or other treatments for 3 months.

We virtually recruited 275 adults from 41 states within the continental United States with olfactory loss diagnosed within 2 weeks of COVID-19 infection lasting for ≥3 months. All participants completed UPSIT before and after treatment at home. All participants sniffed four essential oils daily for 3 months (15 s each, 30 s rest in between). Physician-assigned odors were rose, lemon, eucalyptus, and clove. Patient-preferred odors were four scents chosen from 24 available options. The bimodal arms were also shown digital images of the essential oil they were smelling through a study website. After 3 months, the mean change in UPSIT and ODOR was similar across arms. However, 18/34 (53%) patients in the bimodal, patient-preferred arm compared to only 5/21 (24%) in the control arm, met the MCID for improvement on UPSIT of ≥4 points (difference 29%, 95% CI: 4%–54%). All arms had a higher improvement rate on UPSIT than controls, with 15/37 (41%) in the bimodal, physician-assigned arm, 12/40 (30%) in the unimodal, patient-preferred arm, and 11/38 (29%) in the unimodal, physician-assigned arm. Furthermore, 4/21 (19%) controls reported improvement on CGI-I compared with 12/34 (35%) participants in the bimodal, patient-preferred arm (difference 16%, 95% CI: −7%–39%). These results suggest a benefit to olfactory retraining in COVID compared to no treatment, with a potential but not definitive additional benefit from a bimodal approach with patient-preferred scents.

Efficacy of gabapentin for post-COVID-19 olfactory dysfunction (Gabapentin for the Relief of Acquired Chemosensory Experience [GRACE])

This was a double-blinded, randomized placebo-controlled trial of oral gabapentin for COVID-related OD. Gabapentin is used to treat numerous peripheral neuropathies including diabetic neuropathy, postherpetic neuralgia, chronic pain, and burning mouth syndrome.[13,14] One case series identified gabapentin as a potential treatment for COVID-related parosmia.[15] In this trial, we randomized 68 patients with ≥3 months of COVID-related OD to gabapentin or placebo. Gabapentin was titrated to a maximum tolerable dose, maintained for an 8-week fixed-dose period, and then tapered for 4 weeks. We found no difference in subjective olfactory function on CGI-I after the fixed-dose period of gabapentin, with a response rate of 44% and 46% in the gabapentin and placebo arms, respectively. Changes in objective odor identification on UPSIT, CGI-S for parosmia, and olfactory-related quality of life on ODOR were neither clinically meaningful nor statistically significantly different between the two arms. These results suggest that gabapentin should not be considered a therapeutic agent for COVID-related OD.

SCENT trials

Phosphodiesterase inhibitors, such as theophylline, have been theorized to improve olfaction by preventing breakdown of intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which promote sensory axonal regeneration.[16] Nasal mucous cAMP and cGMP levels are lower in hyposmic participants than normosmic controls,[17] and an increased

TABLE 1 Recent clinical trials in COVID-related olfactory dysfunction at Washington University in St. Louis.

Study, year	Design	Treatment	Subjects	Outcomes (primary[a])	Findings
VOLT, 2022	RCT 2 × 2 factorial	Visual-olfactory retraining versus olfactory retraining alone, assigned (rose, lemon, eucalyptus, clove) versus patient-preferred scents (choice of 4 of 24) daily × 3 months. Control was no treatment	275 adults, OD within 2 weeks of COVID infection, lasting ≥3 months, of whom 170 completed the study: 40 unimodal patient-preferred scents, 38 unimodal physician-assigned scents, 34 bimodal patient-preferred scents, 37 bimodal physician-assigned scents, 21 controls	Change in UPSIT,[a] change in ODOR, CGI-I	Mean change in UPSIT similar across arms with marginal mean diff. for patient-preferred versus assigned scents 0.73 (95% CI: −1.10 to 2.56), bimodal versus unimodal 1.10 (95% CI: −2.92 to 0.74). However, five (24%) controls versus 18 (53%) in bimodal patient-choice arm had MCID improvement in UPSIT (diff. 29%, 95% CI: 4%–54%). 4/21 (19%) controls versus 12/34 (35%) in bimodal patient-choice arm were responders on CGI-I (diff. 16%, 95% CI: −7% to 39%). Mean change in ODOR was 11.6 points (95% CI: 9.2–13.9) and was not clinically or statistically significant difference between arms
GRACE, 2022	RCT, double blinded	Gabapentin versus placebo titrated over 4 weeks from 300 mg TID to maximum tolerated dose up to 1200 mg TID, FD for 8 weeks, taper for 4 weeks	68 adults, OD ≥ 3 months after COVID, UPSIT 6-33 (male) or 34 (female). 44 completed the trial (26 placebo, 18 gabapentin)	CGI-I,[a] change in UPSIT, ODOR, NASAL7, CGI-S, CGI-P at end of 4-week taper. CGI-I at end of 8-week FD	8/18 (44%) in gabapentin arm and 12/26 (46%) controls were responders on CGI-I (diff. 1.7%, 95% CI: 31.6%–28.2%). Mixed model analysis with no clinically meaningful or statistically significant difference in any outcome between gabapentin and placebo groups
SCENT2, 2022	RCT, double blinded	Theophylline 400 mg versus placebo in saline nasal rinse BID × 6 weeks	51 adults, with OD ≥ 3 months after COVID. 45 finished the trial (23 placebo, 22 theophylline)	CGI-I,[a] change in UPSIT, QOD-NS, SF36	13 (59%) theophylline versus 10 (43%) controls were responders on CGI-I (diff. 15.6%, 95% CI: −13.2%–44.5%). 11 (50%) theophylline versus 6 (26%) controls had MCID change in UPSIT (diff. 24%, 95% CI: −4%–52%)
SCENT3, ongoing	RCT, double blinded	Theophylline 400 mg versus placebo in saline nasal rinse BID × 12 weeks	Adults with OD ≥ 3 months after COVID, UPSIT 6–33 (male) or 34 (female)	CGI-I,[a] change in ODOR	Results pending
SGB, 2023	Case series	Bilateral stellate ganglion block injections with mepivacaine performed 1 week apart	20 adults with OD ≥ 12 months after COVID	CGI-I for smell loss,[a] CGI-I for parosmia, change in UPSIT and ODOR, patient satisfaction. All at 1 week after first injection, 1 month after second	At 1-month follow-up, 10 (50%) responded on CGI-I smell loss, 11 (55%) had at least MCID in smell identification using the UPSIT, 11 (55%) had a clinically meaningful improvement on UPSIT, with median difference between UPSIT scores at baseline and 1-month was six (95% CI: 3 –11). 7 (35%) had a clinically meaningful improvement on ODOR

TABLE 1 (Continued)

Study, year	Design	Treatment	Subjects	Outcomes (primary[a])	Findings
SGB 2, ongoing[b]	RCT, patient-blinded	Unilateral stellate ganglion block injection with mepivacaine	Adults with OD ≥ 12 months after COVID	To be determined	Results pending
MBSR, ongoing[b]	RCT	Virtual mindfulness-based stress reduction program versus lifestyle intervention program (ex. physical activity, cooking, sleep hygiene, financial education) for 2 h per week × 8 weeks	Adults with parosmia ≥3 months after COVID infection, excluding those with poorly controlled psychiatric illness	CGI-I for parosmia,[a] CGI-I for smell loss, DisODOR, SCS, DASS-21, Acceptability Questionnaire, CEQ-P	Results pending

Abbreviations: BID, twice daily; CEQ-P, Credibility and Expectancy Questionnaire—Parosmia; CI, confidence interval; CGI-I, Clinical Global Impression of Improvement; CGI-P, Clinical Global Impression Parosmia; CGI-S, Clinical Global Impression of Severity; DASS-21, depression, anxiety, stress scale; Diff., difference; DisODOR, Parosmia Olfactory Dysfunction Outcomes Rating; FD, fixed-dose; GRACE, Gabapentin for the Relief of Acquired Chemosensory Experience; MBSR, mindfulness-based stress reduction; NASAL7, Novel Anosmia Screening at Leisure; OD, olfactory dysfunction; ODOR, Olfactory Dysfunction Outcome Rating; PVOD, postviral olfactory dysfunction; QOD-NS, Questionnaire of Olfactory Disorders—Negative Statements[12]; RCT, randomized controlled trial; SCENT, Smell Changes and Efficacy of Nasal Theophylline; SCS, Smell Catastrophizing Scale; SF-36, 36-Item Short Form Survey; SGB, Stellate ganglion block; TID, three times daily; UPSIT, University of Pennsylvania Smell Identification Test; VOLT, Visual-Olfactory Training.

[a]Primary outcome.

[b]Unpublished.

severity of OD is associated with decreased levels of nasal mucous cAMP and cGMP levels.[18] Oral theophylline for OD in the pre-COVID era showed subjective improvement starting at 4–6 weeks but with continuing improvement for 6–72 months of treatment.[19] Though systemic theophylline has a narrow therapeutic index, intranasal theophylline has been studied at doses that do not increase serum theophylline levels.[20] A study on OD of various etiologies demonstrated improved smell detection and recognition thresholds after 2 months of 20 μg intranasal theophylline spray.[20] Two pilot studies of participants who had PVOD refractory to multiple treatments reported statistically significant improvement in quantitative subjective scores of smell.[20,21]

We conducted initial studies of nasal theophylline in the setting of PVOD of any etiology before the COVID-19 pandemic. SCENT was a randomized, placebo-controlled trial of 12 mg theophylline added to nasal saline irrigations for patients with PVOD for 6–36 months.[10] Nasal irrigation likely improves drug delivery to the olfactory cleft compared to nasal spray or oral formulations. Patients rinsed twice daily for 6 weeks. The rate of improved smell on CGI-I at the end of the intervention was similar in the theophylline and placebo group (33% vs. 30%, difference 3.3%, 95% CI: −35.6%–42.3%). The median differences in pre- and posttreatment UPSIT and Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS)[12] change between the two groups were 1 (95% CI: −3–5) and −10 (95% CI: −15 to −4), respectively, in favor of theophylline. Three patients receiving theophylline and two receiving placebo had clinically meaningful improvements on the UPSIT (between-group differences in the rate of responders 5%, 95% CI: −30% to 40%).

Acknowledging the imprecise estimates of the treatment response rate and the particularly low dose of theophylline used in this trial, we conducted a follow-up study increasing the theophylline dose. This was a phase 1, open-label, dose-escalation trial in 11 patients with PVOD from the SCENT trial.[22] Patients were started on twice daily irrigations of 100 mg theophylline for 7 days, then were advanced 200, 300, and 400 mg per irrigation for each subsequent week. Adverse events were monitored and subjects with severe adverse events were not advanced to a following week with a higher theophylline dose. The maximum daily dose tested was 800 mg to stay below 900 mg, which was among the highest daily oral doses of theophylline used in a published study.[23] Daily nasal irrigations with 800 mg theophylline correspond to a systemic daily dose of 20 mg, which is much lower than the starting oral dose of 300 mg when used for pulmonary disorders. Outcomes were adverse effects, CGI-I, change in UPSIT, and QOD-NS at the end of 4 weeks. One patient withdrew after 3 weeks of treatment due to insomnia, tremors, abdominal pain, and rash. One patient-reported transient light-headedness for 1 day. Of note, four out of 10 participants who completed the 4-week regimen reported improved smell on CGI-I, while the remainder had neither better nor worse smell. Two participants had clinically meaningful improvements on UPSIT, while one had clinically meaningful worsening and the rest had no clinically meaningful change.

In the subsequent SCENT-2 trial, we tested a 6-week course of 400 mg theophylline in saline irrigations twice daily compared to placebo for COVID-related OD.[9] Systemic absorption was measured by serum theophylline in 10 individuals after 1 week of treatment and was negligible in all patients. Of 45 participants who completed the study, 11 of 22 (50%) participants in the theophylline arm compared to six (26%) in the placebo arm had a clinically meaningful change on UPSIT. Of the participants in the theophylline arm 13 (59%) had subjective improvement compared to 10 (43%) in the placebo arm, for a difference in response rate of 15.6% (95% CI: −13.2%–44.5%). This wide CI lacks statistical significance and precludes definitive conclusion. However, the effect size upper bound of 44.5% is much larger than the MCID of 25%, suggesting that the observed effect of theophylline on both subjective and objective outcomes warranted a larger trial to investigate the efficacy of this treatment more fully.

In an effort to increase potential treatment efficacy and decrease the relatively high 43% placebo response rate, we designed the SCENT3 trial, which tests a longer 12-week course of 400 mg theophylline versus placebo irrigations twice daily.[24] The rationale for a longer treatment course was that in nonrandomized placebo-controlled trials of PVOD, OT was observed to improve subjective smell ratings at 8–16 weeks of treatment, with additional incremental improvements with continued treatment up to 24–56 weeks.[25,26] This virtual trial is currently enrolling subjects with COVID-related OD for ≥3 months and with a screening UPSIT score consistent with decreased olfactory function (≤34 in women and ≤33 in men). The primary outcome of this study is response to treatment as defined by CGI-I at the end of 12 weeks of treatment.

Stellate ganglion block (SGB)[27]

The SGB has been used to treat posttraumatic stress disorder, migraine, and complex regional pain syndrome by inhibiting sympathetic neuronal connections and reducing circulating adrenal hormone levels.[28–30] Persistent COVID symptoms may be partially due to feedback loops between hyperactivity of the autonomic nervous system and hyperresponsiveness of the immune system, with case reports describing SGB to successfully treat prolonged COVID-19 symptoms.[31–34] In this single-arm, open-label, prospective case series, 20 adults with COVID-related OD for ≥12 months underwent bilateral SGB. The primary outcome was CGI-I at 1 month after completion of SGB. At 1 month, 10 (50%) participants reported at least slightly improved OD on CGI-I. Furthermore, 11 (55%) had a clinically meaningful improvement in smell identification using the UPSIT, and seven (35%) experienced a clinically meaningful improvement on ODOR. The median difference between UPSIT scores at baseline and 1 month was 6 (95% CI: 3–11), exceeding the MCID of 4. There were no serious adverse events. Given the promising results of the initial SGB data, we are starting a randomized controlled trial (RCT) of SGB compared to a sham injection in patients with parosmia.

MBSR[35]

Many patients with COVID-related OD report that parosmia is psychologically distressing.[36,37] In our anecdotal experience, many patients find distortion of smell more disturbing than loss of smell. MBSR is a psychological therapeutic intervention that emphasizes the focused, nonjudgmental awareness of present-moment experiences without efforts being made to alter or avoid them. It is a form of meditation practice that is embedded in mind/body and integrative medicine to cultivate psychological and emotional resilience. Meta-analyses have suggested that meditation, including MBSR, can improve anxiety, depression, insomnia, and other stress-related outcomes in clinical trials of various conditions including chronic pain, irritable bowel syndrome, tinnitus, cancer, and multiple sclerosis.[38,39] Therefore, the purpose of this trial is to determine if participation in an 8-week MBSR course can impact olfactory-related quality of life compared to a placebo course (lifestyle intervention course without meditation). The primary outcome is CGI-I in which subjects are asked "Compared to the start of the study, how would you rate how intrusive smell distortion (change) is in your life after 8 weeks of treatment?" Data collection for this study is ongoing.

CHALLENGES AND LIMITATIONS

All trials described were conducted at a single tertiary academic institution and many recruited patients through similar techniques, namely the Washington University School of Medicine Volunteers for Health Research Participant Registry, the Otolaryngology Research Participant Registry, and advertisements posted in the Washington University School of Medicine Department of Otolaryngology–Head and Neck Surgery outpatient clinics. This may limit the generalizability of our findings to other institutions or settings. Furthermore, subjects were not excluded based on prior attempts at treatment for COVID-related OD, therefore, patients who were nonresponders to treatment in one trial were permitted to subsequently enroll in another, potentially biasing results toward nonresponse in the more recently conducted trials.

We have also observed a relatively high placebo response rate of >40% in the two completed placebo-controlled medication RCTs (GRACE and SCENT2), which may be due to a placebo effect alone or may reflect the natural recovery of COVID-related OD. This presents a challenge in identifying potential interventions and powering trials for both a clinically meaningful and statistically significant treatment effect.

CONCLUSION

Several novel PROM and therapeutic strategies have been developed and tested for COVID-related OD. These interventions range from smell retraining therapy techniques, systemic pharmacologic therapy, topical therapy, nerve blocks, and mindfulness techniques. To date,

there is no best practice treatment that definitively performs better than placebo for olfactory outcomes. Further research on the mechanisms of COVID-related OD and potential therapies is needed to substantially improve olfactory outcomes in affected patients.

AUTHOR CONTRIBUTIONS

Theresa Tharakan, Dorina Kallogjeri, and Jay F. Piccirillo substantially contributed to the conception, design, analysis, drafting, and interpretation of this work. All authors approve the final manuscript to be published.

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CONFLICTS OF INTEREST STATEMENT

Dr. Piccirillo receives a stipend for serving as Editor-in-Chief of *JAMA Otolaryngology-Head & Neck Surgery* and royalty payments from Washington University for licensing of the SNOT, SNORE, and NOSE HHT instruments. Dr. Kallogjeri receives a stipend for serving as statistics editor for *JAMA-Otolaryngology Head and Neck Surgery*. The remaining author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available upon request from authors.

ETHICS STATEMENT

This review was determined to be not human subjects research by the Washington University Institutional Review Board (IRB ID# 202312044).

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