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# Olfactory Training for Postviral Olfactory Dysfunction: Systematic Review and Meta-analysis

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## Abstract

*Objective.* Olfactory dysfunction is a common problem that is most frequently attributed to upper respiratory infection. Postviral olfactory dysfunction (PVOD) can be prolonged and clinically challenging to treat. Olfactory training (OT) has demonstrated potential benefit for patients with nonspecific olfactory dysfunction. We sought to evaluate the efficacy of OT specifically for PVOD by pooled analysis of the existing evidence.

*Data Sources.* PubMed, Embase, and Web of Science.

*Review Methods.* Following PRISMA guidelines, PubMed, Embase, and Web of Science databases were queried and abstracts screened independently by 2 investigators. We included studies evaluating the efficacy of OT for PVOD and excluded studies evaluating pharmacologic interventions or olfactory loss from other causes.

*Results.* Of the initial 1981 abstracts reviewed, 16 full-text articles were included. Sniffin' Sticks olfactory testing results were reported in 15 (93%) studies as threshold (T), discrimination (D), and identification (I) subscores and TDI total scores. All studies reported clinically significant results after OT, defined as a score improvement of TDI $>5.5$. Four studies were included in the meta-analysis, in which pooled estimates revealed that patients with PVOD who received OT had a 2.77 (95% confidence interval, 1.67-4.58) higher odds of achieving a clinically important difference in TDI scores compared to controls.

*Conclusion.* Meta-analysis of existing data demonstrates clinically significant improvements in PVOD associated with OT. Variability exists among OT protocols and may benefit from further optimization. Existing data supports the use of OT for the treatment of existing and newly emerging cases of PVOD.

## Keywords

olfactory dysfunction, anosmia, olfactory training, viral infection, postviral olfactory dysfunction, COVID-19, systematic review, meta-analysis

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Viral infections of the upper respiratory tract constitute one of the most common causes of outpatient health care visits worldwide.[1] Olfactory dysfunction has been noted as a common symptom in 18% to 22% of cases attributed to a viral etiology.[2] Nasal and paranasal sinus disease constitutes another 21% of the etiologies of olfactory dysfunction.[3] Of these patients, between 66% and 94% eventually experience a spontaneous improvement in olfaction, although a significant proportion of patients continue to experience prolonged olfactory dysfunction.[2,4] Despite most patients reporting some subjective recovery of olfactory function, only about one-third of patients achieve subjective normosmia.[5]

Postviral olfactory dysfunction (PVOD), the most common etiology of olfactory dysfunction, is believed to occur as a result of conductive dysfunction caused by mucosal edema as well as sensorineural dysfunction from degeneration of the olfactory epithelium.[6] PVOD has become especially relevant with the onset of the coronavirus disease 2019 (COVID-19) pandemic, in which viral involvement of olfactory neuroepithelium has resulted in an unprecedented incidence of olfaction loss worldwide.[7,8] Pharmacologic management ranges from corticosteroids to intranasal calcium buffers, although current evidence does not support the use of any particular pharmacologic agent for PVOD.[9]

Olfactory training (OT) is an emerging nonpharmacologic therapy option involving repeated odor exposure that has shown promise in the treatment of olfactory dysfunction. Since 2009, 2 meta-analyses have supported the efficacy of OT for olfactory dysfunction from multiple etiologies (not specific to PVOD).[10,11] A number of individual studies evaluating OT for

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**Table 1.** Database Search Strategy Used for Systematic Review of Olfactory Training for Postviral Olfactory Dysfunction.[a]

| Search terms |
|---|
| TOPICS: post viral olfactory dysfunction OR post viral olfactory disorder OR post viral olfactory loss OR PVOL OR PVOD OR post infectio* olfactory dysfunction OR post infectio* olfactory disorder OR PIOD OR post viral smell loss OR post viral anosmia OR post infectio* anosmia OR post infectio* olfactory loss |
| AND |
| TOPICS: (olfactory training) OR TOPIC: (olfactory therapy) OR TOPIC: (smell training) OR TOPIC: (smell therapy) |

[a]Search terms consisting of topics rather than keywords to broaden the initial database query.

PVOD have emerged in recent years, which, along with current relevance to the global health landscape, have prompted an updated synthesis of available evidence. The primary objective of this systematic review and meta-analysis is to evaluate the efficacy of OT for PVOD, as reflected by changes in patient-reported and clinically measured olfactory function.

## Methods

A systematic review with meta-analysis was conducted consistent with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard on the efficacy of OT for patients with PVOD.[12]

### *Protocol and Registration*

The protocol for this review was accepted to the PROSPERO registry on April 23, 2020 (registration CRD42020180311).

### *Information Sources and Search Strategy*

A comprehensive search of PubMed, Embase, and Web of Science databases was performed on April 23, 2020, with no filters for language or date. Keywords pertaining to the purpose of this review included *olfaction disorders, post viral olfactory dysfunction, post viral olfactory loss, post viral anosmia, post infectious olfactory dysfunction, post infectious olfactory loss*, or *post infectious olfactory anosmia*, and *olfactory training, smell training, smell therapy*, or *olfactory therapy*. Various combinations of keywords were used in searches with ''AND/OR'' as connecting terms to refine results. The comprehensive search strategy used to query each database is described in **Table 1**.

### *Study Selection and Eligibility Criteria*

We included studies that evaluated OT for patients with olfactory dysfunction attributed to viral illness and excluded studies that included patients with olfactory dysfunction attributed to medications, chronic autoimmune disease, chronic neurodegenerative disease, head trauma or traumatic brain injury, inherited syndromes, or iatrogenic causes. Randomized controlled trials and observational studies investigating the role of OT with outcomes pertinent to PVOD were included. Case reports, case series, and population studies were excluded. Abstracts were reviewed independently by 2 reviewers (N.K., T.M.D.) with the assistance of a third reviewer (G.D.U.) to resolve any conflicts.[13] Full-text articles underwent further screening to determine eligibility for inclusion. A PRISMA flow diagram of this process is presented in **Figure 1**.

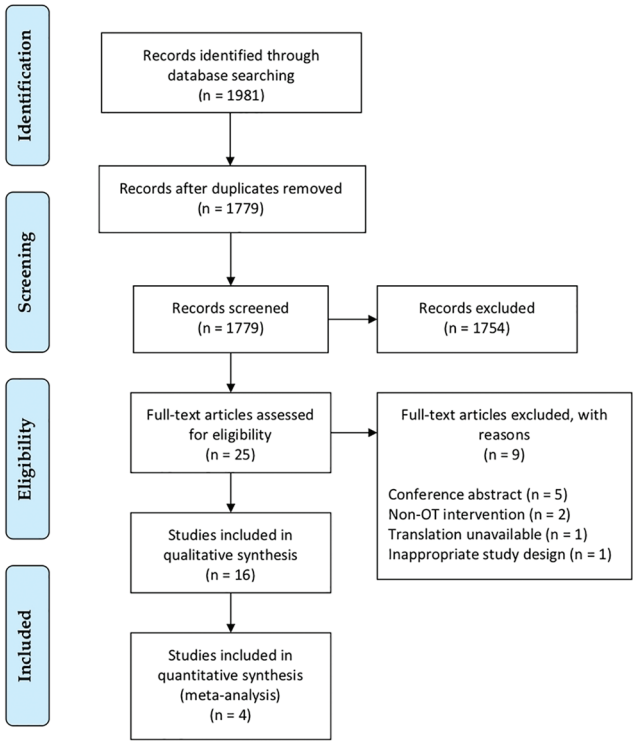


**Figure 1.** PRISMA flow diagram of the systematic review process of olfactory training for postviral olfactory dysfunction. OT, olfactory training.

### *Data Collection*

Two reviewers (T.M.D., N.K.) each manually extracted data, with a third reviewer (G.D.U.) cross-checking the extraction data from each study to maximize accuracy. Data extracted from each study included (1) descriptive baseline characteristics, (2) intervention data (regimen, duration, quality of odors), and (3) outcome measures.

### *Risk of Bias in Individual Studies*

Risk of bias in randomized controlled trials was assessed by the Cochrane Collaboration's instrument, encompassing descriptions of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias.[14]

**Table 2.** Characteristics of Included Studies in the Systematic Review of Olfactory Training for Postviral Olfactory Dysfunction.

| Study | Design | n | Intervention | OT duration |
|---|---|---|---|---|
| Altundag et al (2015)[22] | Randomized controlled trial | 48 | MOT vs COT | 9 mo |
| Damm et al (2014)[24] | Randomized controlled trial | 46 | High-concentration odors vs low-concentration odors | 4.5 mo |
| Fleiner et al (2012)[25] | Prospective cohort study | 16 | COT alone vs COT and corticosteroids | 8 mo |
| Geißler et al (2014)[18] | Prospective cohort study | 39 | COT | 8 mo |
| Gellrich et al (2018)[26] | Prospective case-control study | 61 | COT | 3 mo |
| Hummel et al (2009)[16] | Prospective cohort study | 24 | COT | 3 mo |
| Hummel et al (2017)[27] | Retrospective cohort study | 170 | COT | 3 mo |
| Kollndorfer et al (2015)[17] | Prospective cohort study | 10 | COT alone vs COT and vitamin A | 3 mo |
| Konstantinidis et al (2013)[28] | Prospective cohort study | 81 | COT | 4 mo |
| Konstantinidis et al (2016)[19] | Prospective cohort study | 111 | Short-term COT vs long-term COT | 4 mo, 14 mo |
| Oleszkiewicz et al (2018)[29] | Prospective cohort study | 57 | Simple OT vs complex OT vs odor-altering OT | 6 mo |
| Patel et al (2017)[23] | Randomized controlled trial | 43 | Patient-selected essential oils OT | 6 mo |
| Poletti et al (2017)[30] | Prospective cohort study | 96 | High-molecular-weight OT vs Low-molecular-weight OT | 5 mo |
| Qiao et al (2019)[21] | Prospective cohort study | 60 | COT | 6 mo |
| Qiao et al (2020)[20] | Prospective cohort study | 125 | Combination 1 OT vs combination 2 OT | 6 mo |
| Saatci et al (2020)[31] | Prospective cohort study | 60 | Olfactory training ball vs COT | 3 mo |

Abbreviations: COT, classical olfactory training; MOT, modified olfactory training; OT, olfactory training.

Risk of bias for nonrandomized studies was assessed through the validated Methodological Index of Nonrandomized Studies (MINORS) criteria.[15] Articles were reviewed by 2 authors (N.K., G.D.U.) and scored out of a total of 16 or 24 (if the study was comparative). Each item was scored as 0 for not reported, 1 for reported but inadequate, and 2 for adequate. The final score was an average of the total scores of both reviewers.

### *Meta-analysis*

Controlled studies were included that evaluated OT in patients with PVOD and reported threshold, discrimination, and identification (TDI) scores as outcome measures. Studies that lacked control groups or reported insufficient data were excluded. The meta-analysis was performed with RevMan software (version 5.3.5; Cochrane Group, London, UK). Forest plots were generated for odds of minimal clinically important difference (MCID) between TDI scores, using a fixed-effects model to calculate the odds ratios (ORs) between experimental and control group scores. Study heterogeneity was reported using the $I^2$ statistic.

## Results

### *Study Characteristics*

Of 1981 articles initially reviewed by title and/or abstract, we identified 25 for full-text screening. Of these 25 articles screened, 16 met criteria for qualitative synthesis, and 4 of these were appropriate for meta-analysis (**Figure 1**). The most common reasons for exclusion were conference abstract and non-OT intervention. Among the included studies, 3 were noncomparative observational studies, 10 were comparative observational studies, and 3 were randomized controlled trials (**Table 2**).[16-31] The included studies involved a total of 990 participants, with disease duration ranging from 4 months to 20 years. Fourteen of 16 studies reported on the distribution of sex, skewing toward female patients, with a total of 559 females and 372 males.

Eleven studies evaluated the efficacy of classical olfactory training (COT), and 7 studies evaluated modified olfactory training (MOT), including 2 studies that compared both interventions. For the purpose of this review, COT was defined as the regimen described by Hummel et al,[32] which involves twice-daily exposure to a set of 4 odors, including rose, eucalyptus, lemon, and cloves, from media such as brown jars or markers. Patients typically smell each odorant for 10 seconds or longer, rotating through each until they have finished the entire set. Olfactory function was then assessed at various time points through the Sniffin' Sticks olfactory test kit. Composite TDI scores and constituent T, D, and I subscores were the main outcome measures of olfactory function in 15 of 16 included studies. Longer durations of olfactory dysfunction were associated with less improvement on olfactory function testing, although PVOD patients were also shown to benefit the most from OT when compared with cohorts with different causes of olfactory dysfunction.[22-25,29]

The proportion of patients who achieved MCID was reported in 15 studies and ranged from 6.3% to 70%. MCID was defined as a $>5.5$ or $>6$ increase in TDI scores by the individual study authors. In 2006, Gudziol et al[33] demonstrated that an increase of 5.5 points in TDI composite scores corresponded to more than 60% of patients reporting subjective olfactory improvement; 4 studies use this value as

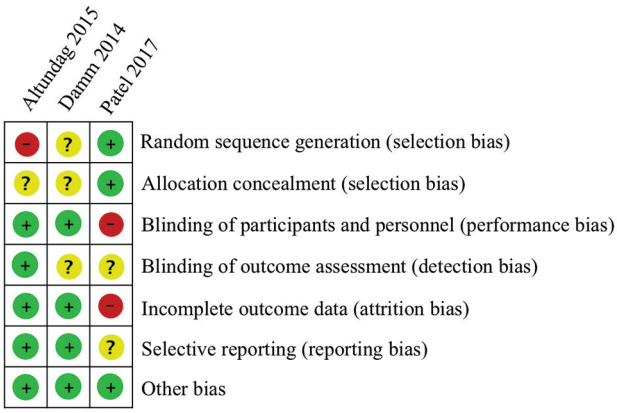


**Figure 2.** Assessment of experimental studies using Cochrane Collaboration's Risk of Bias tool. Plus sign indicates low risk of bias; question mark, unclear risk of bias; minus sign, high risk of bias.

the MCID. In 2009, Hummel et al[16] adopted a change in TDI score of 6 for the MCID, although evidence was not provided to support this new threshold. Ten studies used a change in TDI scores of 6 as the MCID.[16,18-22,24,25,28,29] In 1 randomized controlled trial, the University of Pennsylvania Smell Identification Test (UPSIT) was used as an outcome measure, with MCID defined as a >10% increase in UPSIT score, although evidence provided to support this threshold was not substantial.[23]

## *Risk of Bias Within Studies*

MINORS criteria items to assess risk of bias are presented in **Table 3**. Overall quality was moderate and included 13 studies. The mean (range) MINORS score was 10.5 (9-11.5) for noncomparative studies and 18.7 (16-21) for comparative studies. Common weaknesses in these studies included loss of patients to follow-up and lack of prospective calculation of sample size. Risk of bias was heterogeneous for all 3 randomized controlled studies (**Figure 2**). An assessment of publication bias was not performed given the small number of studies included.

## *Classical Olfactory Training*

Eight controlled and 3 noncontrolled observational studies investigated the efficacy of COT, including 2 studies that compared COT and MOT (**Table 4**).[22,29] Significant improvements in TDI scores postintervention were reported in all studies. However, improvements in subscores demonstrated greater variance than TDI total scores, with no studies reporting significant increases in all 3 subscores. Regimens lasted from 3 to 14 months, with 4 studies reporting scores at various time points to evaluate the relationship between duration of training and efficacy. Longer durations were often associated with greater efficacy of OT.[18-21]

## *Modified Olfactory Training*

Five comparative observational studies and 2 randomized controlled trials introduced modifications to the COT regimen, including using patient-purchased essential oils, varying

**Table 3.** Methodological Index for Non-randomized Studies (MINORS) Evaluating Olfactory Training for Postviral Olfactory Dysfunction.

| | Fleiner et al (2012)[25] | Geißler et al (2014)[18] | Gellrich et al (2018)[26] | Hummel et al (2009)[16] | Hummel et al (2017)[27] | Kollndorfer et al (2015)[17] | Konstantinidis et al (2013)[28] | Konstantinidis et al (2016)[19] | Oleszkiewicz et al (2018)[29] | Poletti et al (2017)[30] | Qiao et al (2019)[21] | Qiao et al (2020)[20] | Saatci et al (2020)[31] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total score | 9 | 11 | 17 | 20.5 | 18 | 18.5 | 21 | 20 | 16 | 18 | 11.5 | 17 | 21 |
| Clearly stated aim | 1 | 1 | 2 | 2 | 1.5 | 1.5 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Inclusion of consecutive patients | 1 | 1 | 1 | 2 | 1.5 | 2 | 2 | 2 | 2 | 2 | 1.5 | 2 | 2 |
| Prospective collection of data | 1.5 | 2 | 2 | 2 | 1.5 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Endpoints appropriate | 2 | 2 | 1.5 | 2 | 2 | 2 | 2 | 2 | 1.5 | 2 | 2 | 1.5 | 2 |
| Unbiased assessment of endpoint | 0.5 | 1 | 1.5 | 1.5 | 1.5 | 1 | 1 | 1 | 0 | 1.5 | 1 | 1 | 1.5 |
| Appropriate follow-up period | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1.5 |
| Loss to follow-up <5% | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1.5 | 1 | 1 | 1 | 2 |
| Prospective calculation of sample | 0 | 0 | 0 | 0.5 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| Adequate control group | — | — | 1.5 | 2 | 1.5 | 1.5 | 2 | 2 | 0.5 | 1 | — | 1 | 1 |
| Contemporary groups | — | — | 2 | 2 | 1.5 | 2 | 2 | 2 | 2 | 2 | — | 2 | 2 |
| Baseline equivalence groups | — | — | 1 | 2 | 1 | 1 | 2 | 2 | 0.5 | 1.5 | — | 1.5 | 2 |
| Adequate statistical analyses | — | — | 1.5 | 1.5 | 2 | 1.5 | 2 | 2 | 2 | 2 | — | 2 | 2 |

**Table 4.** Findings of Studies Evaluating Classical Olfactory Training Regimens for Postviral Olfactory Dysfunction.

| Study | PVOD duration (Mean) | TDI score (Mean ± SD) | % Achieving MCID, defined in each study | Conclusions |
|---|---|---|---|---|
| Fleiner et al (2012)[25] | 10.25-30.75 mo (range) | *Pretreatment*:<br>COT: 16.27 ± 9.01<br>COT + steroids: 15.02 ± 9.01<br>*Posttreatment*:<br>COT: 19.20 ± 4.87*<br>COT + steroids: 19.11 ± 7.09 | MCID: >6 increase in TDI score<br>COT only: 1/16 (6.25%)<br>COT + steroids: 4/16 (25%) | In patients with PVOD, COT resulted in significantly greater improvements in TDI scores with little clinical significance; addition of a corticosteroid to COT could enhance efficacy of OT |
| Geißler et al (2014)[18] | 10 mo | *Pretreatment*:<br>COT: 17 ± 5<br>*Posttreatment*:<br>COT: 21 ± 7* | MCID: >6 increase in TDI score<br>COT: 22/39 (56%) | In patients with PVOD, COT resulted in significantly greater improvements in TDI scores at 8 mo as compared with 3 mo |
| Gellrich et al (2018)[26] | 4 mo–20 y (range) | *Pretreatment*:<br>COT: 16.4 ± 3.6<br>*Posttreatment*:<br>COT: 21.9 ± 5.6** | MCID: >5.5 increase in TDI score<br>COT: 16/30 (53.3%) | In patients with PVOD, COT resulted in significantly greater improvements in TDI scores at 12 wk |
| Hummel et al (2009)[16] | Control: 53.3 mo<br>Treatment: 49.2 mo | *Pretreatment*:<br>COT: 19.2 ± 6.4<br>*Posttreatment*:<br>COT: mean 10.3 increase from baseline (no SD reported)* | MCID: >6 increase in TDI score<br>Control: 1/16 (6%)<br>COT: 10/36 (28%) | In patients with PVOD, COT resulted in significantly greater improvements in TDI scores at 3 mo |
| Hummel et al (2017)[27] | 12 mo | *Pretreatment*:<br>COT alone: 22.5 ± 7.1<br>COT + vitamin A: 19.4; 6.0<br>*Posttreatment*:<br>COT alone: 25.0 ± 6.6<br>COT + vitamin A: 23.6 ± 6.1 | MCID: >5.5 increase in TDI score<br>COT: 23%*<br>COT + vitamin A: 37%* | In patients with PVOD, COT and vitamin A resulted in significantly greater improvements in TDI scores at 3 mo vs COT alone |
| Kollndorfer et al (2015)[17] | 4.1 y | *Pretreatment*:<br>COT: 11.82 ± 2.76<br>*Posttreatment*:<br>COT: 13.79 ± 4.21 | Not reported | In patients with PVOD, COT resulted in significantly greater improvements in T subscores but not D subscores or I subscores at 13 wk vs healthy controls |
| Konstantinidis et al (2013)[28] | Control: 8.7 mo<br>Treatment: 9.2 mo | *Pretreatment*:<br>Control: 19 ± 2.3<br>COT: 18.95 ± 2<br>*Posttreatment*:<br>Control: 20.5 ± 2.0*<br>COT: 25.2 ± 1.8* | MCID: >6 increase in TDI score<br>Control: 33%<br>PTOD: 33.2%<br>PVOD: 68% | In patients with PVOD, COT resulted in significantly greater improvements in TDI scores at 4 mo; MCID was achieved in 67.8% of patients with PVOD and 33.2% of patients with PTOD |

*(continued)*

**Table 4.** (continued)

| Study | PVOD duration (Mean) | TDI score (Mean ± SD) | % Achieving MCID, defined in each study | Conclusions |
|---|---|---|---|---|
| Konstantinidis et al (2016)[19] | Short OT: 9.1 mo<br>Long OT: 9.5 mo | *Pretreatment*:<br>Control: 15.2 ± 1.8<br>Short OT[a]: 15 ± 2.2<br>Long OT[a]: 15.9 ± 2.2<br>*Posttreatment*[a]:<br>$Control_4$: 16.5 ± 2.4*<br>$Control_{14}$: 20.5 ± 1.6*<br>$Short_4$: 23.51 ± 2.1*<br>$Short_{14}$: 24.1 ± 1.5*<br>$Long_4$: 23.52 ± 1.8*<br>$Long_{14}$: 27.3 ± 1.5* | MCID: >6 increase in TDI score<br>Control: 37%<br>Short: 58%<br>Long: 71% | In patients with PVOD, long-term COT resulted in significantly greater improvements in TDI scores at 14 mo vs short-term COT |
| Qiao et al (2019)[21] | 13.4 mo | *Pretreatment*:<br>COT: 16.82 ± 2.67<br>*Posttreatment*:<br>COT: 22.48 ± 3.73* | MCID: >6 increase in TDI score<br>COT: 41.67% | In patients with PVOD, COT resulted in significantly higher improvements in TDI scores at 6 mo vs 3 mo |

Abbreviations: COT, classical olfactory training; MCID, minimal clinically important difference; OT, olfactory training; PTOD, posttraumatic olfactory dysfunction; PVOD, postviral olfactory dysfunction; TDI, threshold, discrimination, identification.

[a]Patients in 4-mo and 14-mo OT regimens were also evaluated at 4 mo and 14 mo follow-up.

*$P < .05$; **$P < .01$.

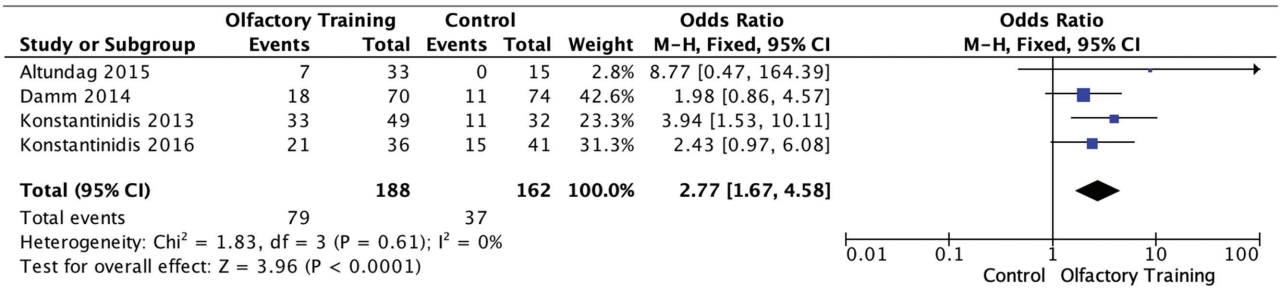


**Figure 3.** Forest plot of meta-analysis comparing odds of achieving a minimal clinically important difference with olfactory training versus controls in patients with postviral olfactory dysfunction. Diamond indicates overall effect estimate; square, point estimate of the study; black line, 95% confidence interval.

odor concentrations and molecular weight, switching the sets of odors every few months, comparing different combinations of odors, and introducing a novel, ergonomic delivery system (**Table 5**).[20,22-24,29-31] Although statistically significant improvements in TDI scores postintervention were reported in all studies except one, evidence supporting modification of odor concentrations, combinations, and molecular weight was mixed.[20,22-24,29,30] Increasing patient compliance and adherence through using patient-purchased essential oils or a more intuitive ''olfactory training ball'' showed more favorable results when compared with no intervention and COT, respectively.[23,31]

### *Meta-analysis*

Four studies met inclusion criteria for meta-analysis. Among these studies, 2 by Altundag et al and Damm et al were randomized controlled trials, and 2 by Konstantinidis et al were prospective nonrandomized controlled studies.[19,22,24,28] Although both studies by Konstantinidis et al evaluated COT, Damm et al and Altundag et al investigated MOT regimens in addition to the COT group.[19,22,24,28] Only the results from the COT regimens were pooled into the meta-analysis to minimize heterogeneity in OT protocols.

The pooled estimate revealed that patients with PVOD who received OT had greater odds of achieving an MCID in TDI scores when compared with controls (OR 2.77; 95% confidence interval [CI] 1.67-4.58; **Figure 3**). Although low heterogeneity was observed with an $I^2$ statistic of 0%, this result was not significant, possibly because of the small number of studies included.

## Discussion

This review is the first to summarize the evidence for OT specifically for the indication of PVOD. Within the context of widespread PVOD due to the COVID-19 pandemic, this topic has become increasingly relevant. Recent meta-analyses have found a beneficial effect from OT on a range of etiologies for olfactory dysfunction, although characterized by a high level of heterogeneity between included studies.[10,11] Our meta-analysis focused only on patients with PVOD treated with OT, which revealed a nearly 3-fold greater odds of achieving an MCID in TDI scores when compared with controls.

Qualitative synthesis revealed that COT is effective for the reduction of symptoms in patients with PVOD, whereas MOT is more effective when focused on increasing patient compliance and adherence, without significant effect from changing odor combinations or concentrations. OT using patient-purchased essential oils produced clinically significant increases of >10% in UPSIT scores for 32% of patients, with excellent compliance reported, a similar result to other studies evaluating COT.[23] However, this 10% threshold was defined with little evidence and acknowledged by the authors as a possible limitation.[23] The efficacy of COT versus MOT was evaluated by Altundag et al[22] and Saatci et al,[31] with both concluding that more patients undergoing modified regimens aimed at increasing patient compliance achieved greater clinically significant improvement in olfactory function than patients undergoing classical regimens.

Ease of implementation and minimal adverse effect profile underscore OT as a favorable mode of therapy for patients with PVOD.[11] Longer duration of OT is associated with greater improvements in olfactory function, whereas longer duration of symptoms is associated with worse outcomes. Even though 12 weeks was the shortest duration of therapy, all 5 studies that used this training period reported clinically significant improvements in olfactory function. To establish a recommended minimum duration, future trials should investigate and compare sequentially shorter OT regimens until patients no longer achieve clinically significant improvements in olfactory function postintervention. Study of long-term OT regimens should also be considered to establish whether benefits with 56 weeks of OT are reproducible.[19]

As this review is focused on PVOD specifically, contributions of heterogeneity from other etiologies of olfactory loss were reduced. Persistently different OT results among studies in this review could be related to variance in OT protocols and COT regimens. Nevertheless, multiple studies report that OT is more effective for PVOD than for other etiologies of olfactory dysfunction.[22-25,29] Interestingly, prior studies have demonstrated decreased metabolism in olfaction centers of the brains of patients with PVOD, suggesting that OT induces changes in functional connectivity of olfactory, somatosensory, and integrative pathways in the brain.[17,34]

Specific pharmacologic therapies for PVOD are lacking, which further supports the contemporary interest in OT as a

**Table 5.** Findings of Studies Evaluating Modified Olfactory Training Regimens for Postviral Olfactory Dysfunction.

| Study | PVOD duration (Mean) | TDI score (Mean ± SD) | % Achieving MCID, defined in each study | Conclusions |
|---|---|---|---|---|
| Altundag et al (2015)[22] | 7.2 mo | *Pretreatment*:<br>COT: 18.2 ± 1.7<br>MOT: 18.1 ± 1.8<br>Control: 18.0 ± 2.3<br>*Posttreatment*:<br>COT: 24.3 ± 3.4**<br>MOT: 26.3 ± 4.2**<br>Control: 19.7 ± 2.3** | MCID: >6 increase in TDI score<br>MOT: 21/37 (56%)<br>COT: 15/33 (46%) | In patients with PVOD, MOT involving alteration of odors every 3 mo resulted in significantly greater improvements in TDI scores at 9 mo than COT |
| Damm et al (2014)[24] | 10.5 mo | *Pretreatment*:<br>High: 17.87 ± 7.09<br>Low: 18.15 ± 6.9<br>*Posttreatment*:<br>High: 21.24 ± 7.29<br>Low: 20.32 ± 6.46 | MCID: >6 increase in TDI scores<br>High concentration OT: 18/70 (25.7%)<br>Low concentration OT: 11/74 (14.9%) | In patients with PVOD, higher-concentration OT showed significantly greater improvements in TDI scores at 4.5 mo than lower-concentration OT |
| Oleszkiewicz et al (2018)[29] | 22 mo | *Pretreatment*:<br>PVOD: 18.3<br>*Posttreatment*:<br>PVOD: 22.5 ± 1.1 | MCID: >6 increase in TDI scores<br>PVOD: 23/57 (40.4%)<br>Idiopathic olfactory dysfunction: 3/51 (5.9%) | In patients with PVOD, there was no significant difference in TDI scores at 6 mo after simple OT, complex OT, and odor-altering OT; more patients with PVOD demonstrate clinically significant improvement than patients with olfactory dysfunction due to idiopathic etiology |
| Patel et al (2017)[23] | 24 mo | UPSIT used instead of TDI | MCID: >10% increase in UPSIT score<br>Control: 2/13 (15.3%)<br>Treatment: 6/19 (31.6%) | In patients with PVOD, patient-purchased essential oils can serve as a cost-effective substitute for OT, although no statistical significance was found for differences in numerical scores at 6 mo |
| Poletti et al (2017)[30] | Not reported | PVOD: TDI score plotted on graph** | MCID: >5.5 increase in TDI scores<br>PVOD: 45%<br>PTOD: 16% | In patients with PVOD, there was no significant difference in TDI score improvements at 5 mo between high-molecular-weight and low-molecular-weight odors used in OT; a significantly higher proportion of patients with PVOD showed clinically significant recovery versus patients with PTOD |
| Qiao et al (2020)[20] | 11.9 mo | *Pretreatment*:<br>Combination 1 (control): 16.82 ± 2.67<br>Combination 2 (test): 16.29 ± 2.69<br>*Posttreatment*:<br>Combination 1 (control): 22.48 ± 3.73*<br>Combination 2 (test): 22.88 ± 3.90* | MCID: >6 increase in TDI scores<br>Combination 1 (control): 41.67%<br>Combination 2 (test): 41.54% | In patients with PVOD, there was no significant difference in TDI score improvements at 6 mo between combinations of odors used in OT |

*(continued)*

**Table 5.** (continued)

| Study | PVOD duration (Mean) | TDI score (Mean ± SD) | % Achieving MCID, defined in each study | Conclusions |
|---|---|---|---|---|
| Saatci et al (2020)[31] | 9.5 mo | *Pretreatment:*<br>COT: 16.2 ± 4.4<br>OTB: 16.1 ± 4.3<br>*Posttreatment:*<br>COT: 19.9 ± 4.7<br>OTB: 22.1 ± 2.8* | MCID: >5.5 increase in TDI scores<br>COT: 9/30 (30%)<br>OTB: 21/30 (70%) | In patients with PVOD, OTB showed significantly higher improvements in TDI scores at 3 mo versus COT |

Abbreviations: COT, classical olfactory training; MCID, minimal clinically important difference; MOT, modified olfactory training; OTB, olfactory training ball; PTOD, posttraumatic olfactory dysfunction; PVOD, postviral olfactory dysfunction; TDI, threshold, discrimination, identification; UPSIT, University of Pennsylvania Smell Identification Test.
*$P < .05$; **$P < .01$.

treatment option. Pharmacologic treatments that have been investigated for PVOD include topical and systemic glucocorticoids, alpha lipoic acid, and caroverine.[9,35] The effectiveness of pharmacologic intervention is believed to be dependent on the etiology of olfactory dysfunction, with systemic glucocorticoids being specifically used regularly for acute and chronic rhinosinusitis. A systematic review conducted by Harless and Liang[9] found no evidence for any particular pharmacologic treatment as sole therapy for PVOD, further highlighting the need for a nonpharmacologic modality of treatment such as OT.[9]

Limitations of this study include the small number of randomized controlled trials available for quantitative analysis. This could be a consequence of the novelty of the therapy and difficulty of appropriate control selection. Some studies used healthy controls with normal baseline olfactory function, which inherently makes comparison to the intervention group difficult as patients with PVOD had a much lower baseline. Differences in handling of the control group could have affected the results, as some studies used placebos of empty jars whereas other studies used no interventions for the control group.

Variations in the specific OT regimens employed and in follow-up intervals may have further affected the results of these studies and contributed to the overall heterogeneity of findings. While differences in regimens and follow-up intervals may affect the efficacy of OT, these variables also may affect patient compliance, introducing additional potentially confounding factors and contributions to study heterogeneity. Despite the heterogeneity in the OT protocols of studies meeting inclusion criteria for meta-analysis, clinically significant improvements in olfactory function were identified in 15 of 16 studies, supporting an overall benefit of OT regardless of study-specific differences in OT protocols.

## Conclusion

OT is associated with a clinically significant improvement in olfactory function among patients with PVOD. Variability exists among OT protocols, which may benefit from further optimization and standardization. Available data suggests that OT should be considered for the treatment of existing and newly emerging cases of PVOD.

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### Author Contributions

**Nrusheel Kattar**, conception and study design, data acquisition, analysis, manuscript preparation, final approval, accountable for all aspects; **Triet M. Do**, study design, data acquisition, analysis, manuscript preparation, final approval, accountable for all aspects; **Graham D. Unis**, study design, data acquisition, analysis, manuscript preparation, final approval, accountable for all aspects; **Matthew R. Migneron**, interpretation, manuscript preparation, critical review and revision of manuscript, final approval, accountable for all aspects; **Andrew J. Thomas**, interpretation, manuscript preparation, critical review and revision of manuscript, final

approval, accountable for all aspects; **Edward D. McCoul**, conception and study design, manuscript preparation, critical review and revision of manuscript, final approval, accountable for all aspects.

## Disclosures

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