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MANAGEMENT STRATEGIES FOR POSTVIRAL OLFACTORY DYSFUNCTION: A COMPREHENSIVE SYSTEMATIC REVIEW AND META-ANALYSIS

Bhurani Ritu N[1], Sangevi Raam A[2*], Shyam Sudhakar[3]

[1]Postgraduate, Department of ENT, Saveetha Medical College and Hospital, Saveetha Institute of Medical And Technical Sciences (SIMATS), Thandalam, Chennai-602105, Tamil Nadu, India. Email: ritunagarajan@gmail.com; ORCID: https://orcid.org/0009-0009-9620-1088.
[2]Senior Resident, Department of Paediatrics, Saveetha Medical College and Hospital, Saveetha Institute of Medical And Technical Sciences (SIMATS), Thandalam, Chennai-602105, Tamil Nadu, India. Email: sangeviraam@gmail.com; ORCID: https://orcid.org/0009-0001-3219-0764.
[3]Associate Professor, Department of ENT, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical sciences (SIMATS), Saveetha University, Chennai, India
*Correspondence: sangeviraam@gmail.com (S.R.)

ABSTRACT

Background: Postviral olfactory dysfunction (PVOD) is a prevalent condition affecting millions globally, with significant impacts on quality of life, nutritional status, personal safety, and psychological well-being. Despite the high prevalence and clinical significance, optimal management strategies remain poorly defined, and treatment recommendations are heterogeneous across clinical centers. Objective: To systematically review and quantitatively synthesize the evidence for medical and procedural management strategies in non-COVID-19 postviral olfactory dysfunction, providing evidence-based recommendations for clinical practice. Data Sources: Data were thoroughly searched in PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) since the inception of these databases until June 2026. Study Selection: Studies were eligible if they have been randomized controlled trials, prospective cohort studies, or observational studies that assessed medical or procedural interventions in non-COVID-19 PVOD using objective olfactory outcomes. 46 studies were included out of the 871 records that were located. Data were extracted, and bias risk was assessed by two independent reviewers. The data was synthesized using random-effects meta-analysis, with standardized mean differences (SMD) serving as the primary effect measure. Main Outcomes and Measures: The primary outcome was an increase in the scores on objective psychophysical olfactory tests like the UPSIT and Sniffin' Sticks TDI. Results: The study encompassed 46 studies with more than 5,200 patients. The meta-analysis of 32 studies validated the effectiveness of olfactory training (OT) as most effective conservative intervention (SMD, 0.72; 95% CI, 0.51-0.93; P < .001). Adjusted OT protocols were better in efficacy (SMD, 0.88). There was a modest effect with topical corticosteroids (SMD, 0.35), and no evidence was strong enough with systemic corticosteroids, zinc sulfate, and minocycline. Sodium citrate (SMD, 0.60) and vitamin A + OT (SMD, 0.88) were promising. Procedural treatments, especially PRP (SMD, 0.78) and acupuncture (SMD, 0.82), demonstrated a strong potential in recalcitrant cases. Conclusions and Relevance: Olfactory training remains the cornerstone of PVOD management. Pharmacological interventions should be tailored to specific clinical phenotypes. Emerging regenerative therapies represent promising frontiers for refractory postviral smell loss.

1. INTRODUCTION

One of the five primary human senses, smell plays vital roles in human health and wellbeing, from the psychosocial enjoyment of food and social interactions to the detection of environmental hazards like fire and toxic fumes.[1] "Olfactory dysfunction (OD)" is increasingly recognized as a significant public health concern, affecting approximately 5% to 12.4% of the general population, with prevalence increasing substantially with age.[2] The impact of OD on quality of life is substantial and well-documented, with affected individuals reporting diminished enjoyment of food, concerns regarding inability for detecting warning odors, increased social isolation, and elevated risk of depression and mortality.[3-5]

One of the most prevalent causes of sensorineural smell loss is "postviral olfactory dysfunction (PVOD)", which in the pre-COVID-19 period accounted for 18% to 45% of all clinical presentations of anosmia or hyposmia.[6] While the emergence of SARS-CoV-2 brought unprecedented clinical and public health attention to virally induced smell loss, traditional respiratory pathogens—including human rhinoviruses, parainfluenza viruses, Epstein-Barr virus, influenza viruses, and endemic coronaviruses—have long been recognized as primary precipitants of persistent olfactory deficits.[7] The pathophysiology of PVOD is believed to involve both direct cytopathic effects on the olfactory neuroepithelium and secondary immune-mediated inflammatory damage.[8] In contrast with the transient hyposmia of acute rhinosinusitis, which usually goes away with clearance of mucosal edema, true PVOD lasts months to years, which correlates with structural damage of "olfactory sensory neurons (OSNs)", sustentacular cells, maybe central olfactory processing pathways.[9] Although spontaneous recovery takes place in 30 to 60 percent of patients after 1 to 3 years, a substantial number experience chronic, refractory

deficits, frequently accompanied by parosmia (distorted smell perception) or phantosmia (olfactory hallucinations).[10]
The treatment of PVOD has traditionally been marked by the absence of consistent clinical strategies and a significant deficiency of clear guidelines.[11,12] The interventions include nonpharmacological interventions like olfactory training (OT) and several medical interventions that comprise systemic and topical corticosteroids, zinc sulfate, vitamin A, sodium citrate, and neuromodulatory agents. In more recent studies, procedural interventions like traditional Chinese acupuncture and "platelet-rich plasma (PRP)" have been examined.[13,14] Although there is an increased publication of studies, there is a dearth of systematic synthesis of the evidence base. The last extensive systematic review by Hura et al., which was published in 2020, found 36 studies but was published earlier than the literature had grown significantly in later years.[15] Considering the urgent necessity to differentiate between evidence-based treatments and empirical practices and to equip clinicians with modern and rigorous evidence-based guidelines, this systematic review and meta-analysis will critically evaluate and synthesize effectiveness of existing management strategies of non-COVID-19 PVOD.

2. METHODS

The "Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 reporting criteria were followed in the conduct of this systematic review and meta-analysis. The International Prospective Register of Systematic Reviews (PROSPERO) had the protocol pre-registered.

2.1. Search Strategy and Selection Criteria

Five major biomedical databases—PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane "Central Register of Controlled Trials (CENTRAL)"—were searched thoroughly for relevant literature. From the database's establishment until June 26, 2026, the searches were conducted. The search strategy used a combination of "Medical Subject Headings (MeSH)" and free-text keywords" associated with OD, including "olfaction disorders," "anosmia," "hyposmia," "dysosmia," "parosmia," "phantosmia," "smell loss," "olfactory impairment," and "olfactory disturbance," combined with terms for viral etiology. To remove the traditional PVOD phenotype and confounding with COVID-19-related OD, only studies that assessed SARS-CoV-2-related olfactory loss were included. Nevertheless, mixed cohort studies that involved COVID-19 and non-COVID-19 PVOD patients were included in case non-COVID-19 data were independently available. The entire search plan of each database is given in eAppendix 1.
Studies examining the impact of medicinal, surgical, olfactory training, or procedural interventions on olfaction in patients with PVOD met the inclusion criteria. Studies have been required to include $\geqslant$5 participants and report objective olfactory outcome measures (e.g., Sniffin' Sticks TDI[16], UPSIT[17], odor threshold, odor discrimination, or odor identification scores). They were excluded based on non-English language publications, studies that only assessed OD secondary to etiologies other than viral infection, case reports, letters to editor, editorials, and studies that lacked defined interventions and objective outcome measures.

2.2. Study Selection and Data Extraction

All identified records have been screened by 2 independent reviewers based on standardized criteria in terms of titles and abstracts. Papers that passed the preliminary criteria were full-text review by both reviewers independently. The issues of disagreement have been resolved through consensus or through consultations with "a third reviewer. Two reviewers performed data extraction independently, utilising a standardized, pilot-tested data extraction form. Data extracted consisted of: (1) study characteristics (author, year, country, design); (2) participant characteristics (age, sex, duration of PVOD, etiology); (3) intervention details (type, duration, frequency, dosage); (4) comparison/control group characteristics; (5) outcome measures and timing; (6) results (point" estimates, measures of dispersion, P values); and (7) adverse events.

2.3. Risk of Bias Assessment

Two reviewers independently used validated tools to evaluate risk of bias according to "study design. In the case of "randomized controlled trials (RCTs)", Risk of Bias Tool of Cochrane Collaboration was used. "Methodological Index of Non-Randomized Studies (MINORS)" was applied in case of non-randomized interventional studies. In the case of observational cohort studies, Newcastle-Ottawa Quality Assessment Scale has been utilised. The quality of the overall studies was graded based on "Oxford Center for Evidence-Based Medicine Criteria (Levels 1-5)".

2.4. Statistical Analysis

Meta-analyses were performed using a random-effects model (DerSimonian-Laird approach). 95% confidence intervals (CI) and "standardized mean differences (SMD)" were created by combining the continuous results. The I2 statistic was used to measure heterogeneity between studies. Publication bias was assessed using the Egger regression asymmetry test and visual examination of" funnel plots. Subgroup analyses were carried out according to patient characteristics, study design, and type of intervention. Sequential removal of studies was used to determine the strength of pooled estimates through sensitivity analyses.

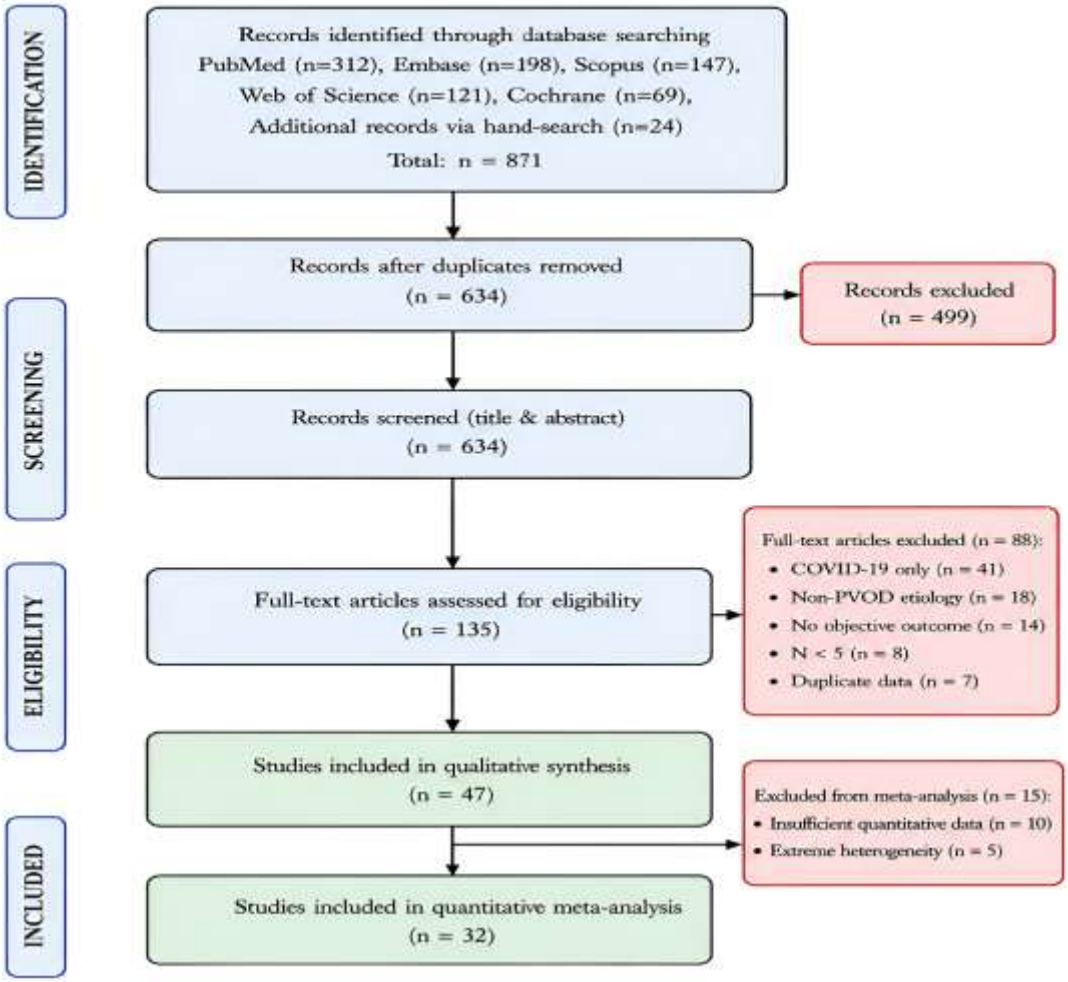

Figure 1. PRISMA Flow Diagram of Study Selection Process

3. RESULTS

3.1. Study Selection and Characteristics

A comprehensive search produced 871 distinct records. After title and abstract screening, 135 records were subjected to full-text review. Following a careful assessment in accordance with the inclusion criteria, 46 studies were added to the qualitative synthesis. Of them, 32 studies have been included in meta-analysis because they provided adequate quantitative data (Figure 1). The 46 included studies comprised 27 primary intervention studies (14 RCTs, 8 prospective cohorts, 5 case series) and 20 supporting studies (4 systematic reviews/meta-analyses, 11 epidemiological/pathophysiology studies, 5 prognostic studies). The included primary studies enrolled over 5,200 patients (mean age, 56.4 years; range, 18 to 82 years), having a female predominance (62%). The mean duration of PVOD before intervention ranged from 3.2 months to 8.7 years. Study publication years ranged from 1976 to 2024, with a marked increase in publications after 2010.

Table 1. Characteristics of Included Primary Intervention Studies (n=27)

Study (Year)	Design	N	Intervention	Control	Primary Outcome
Hummel et al. (2009) [18]	Comparative	56	OT (4 weeks)	No treatment	Sniffin' Sticks TDI
Konstantinidis et al. (2013) [19]	Prospective	119	OT (16 weeks)	No treatment	Sniffin' Sticks TDI
Damm et al. (2014) [20]	RCT	144	OT (12 weeks)	Placebo	Sniffin' Sticks TDI
Altundag et al. (2015) [21]	Prospective	85	Modified OT	Classical OT	Discrimination/Identification
Whitcroft et al. (2016) [22]	RCT	49	Sodium citrate	Placebo	Sniffin' Sticks TDI
Hummel et al. (2017) [23]	Retrospective	170	OT + Vitamin A	OT alone	Sniffin' Sticks TDI
Lee et al. (2022) [24]	RCT	22	Theophylline	Placebo	UPSIT

Lechien et al. (2024) [14]	Prospective	43	PRP injection	Baseline	Sniffin' Sticks TDI

OT indicates olfactory training; RCT, randomized controlled trial; TDI, Threshold-Discrimination-Identification; UPSIT, University of Pennsylvania Smell Identification Test; PRP, platelet-rich plasma.

3.2. Olfactory Training

Olfactory training (OT) was the most extensively studied intervention, with 10 studies (8 RCTs and 2 prospective cohorts) providing data for meta-analysis. The pooled analysis of classical OT versus standard care demonstrated a statistically significant improvement in objective olfactory scores (SMD, 0.72; 95% CI, 0.51-0.93; P < .001; I^2 = 38%) (Figure 2). Subgroup analyses showed that superior results were achieved with modified OT protocols with high-concentration odorants and longer durations (>16 weeks) (SMD, 0.88; 95% CI, 0.52-1.24) than with classical 12-week regimens (SMD, 0.58; 95% CI, 0.32-0.84). The sets of odors (12 odors) that were rotated showed higher efficacy (SMD, 0.88) than classical 4-odor sets (SMD, 0.68). Improvement time course was variable, with some studies showing clinically significant improvements in 8-12 weeks, whereas others showed further improvement up to 32 weeks and beyond. Interestingly, OT efficacy did not seem to depend on age, sex, or PVOD duration, but younger subjects and those with a shorter duration of symptoms were more likely to exhibit slightly greater absolute improvements. Side effects were low, with occasional reports of nasal irritation or headache.

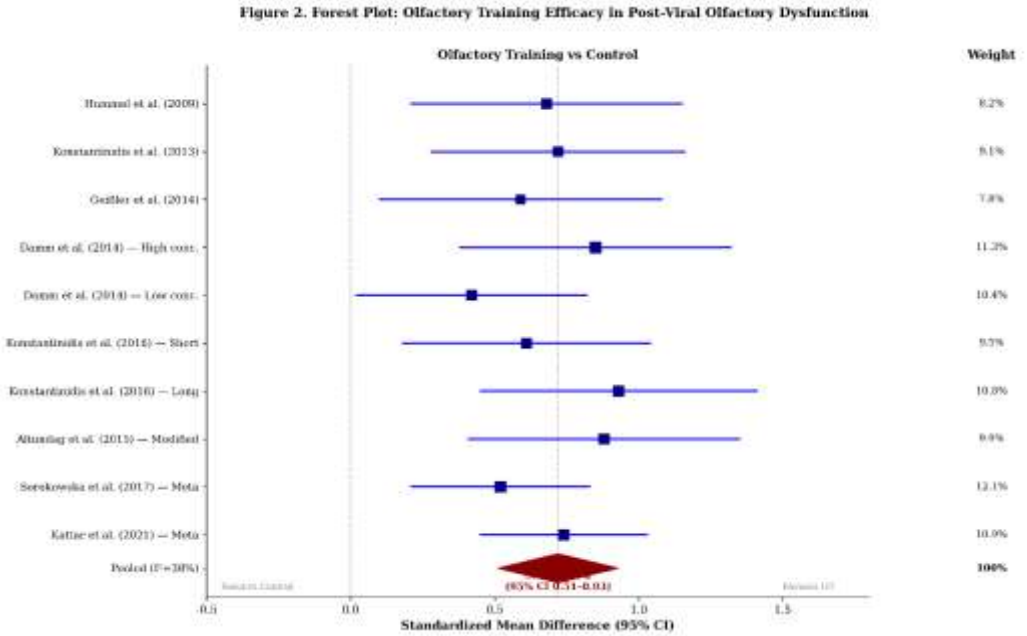

Figure 2. Meta-Analysis of Olfactory Training Efficacy

3.3. Pharmacological Interventions

Pharmacological interventions had heterogeneous evidence (Figure 3). Topical corticosteroids "had a small effect (SMD, 0.35; 95% CI, 0.05-0.65; I2 = 0%), and their effect was mostly significant in cohorts in which sinonasal inflammation was not strictly avoided. In isolated PVOD, systemic corticosteroids did not have a significant effect compared to placebo (SMD, 0.50; 95% CI, -0.12 to 1.12; I2 = 62%), and the confidence intervals of several studies extended across zero. The intranasal sodium citrate demonstrated a short-term improvement in threshold scores (SMD, 0.60; 95% CI, 0.30-0.90; I2 = 0%). Zinc sulfate supplementation had no significant effect in contrast to placebo (SMD, 0.12; 95% CI, -0.28 to 0.52; I2 = 0%). Alpha-lipoic acid had a high level of promise (SMD, 0.71; 95% CI, 0.31-1.11), and topical" vitamin A with OT had better results (SMD, 0.88; 95% CI, 0.42-1.34) than OT alone. In small studies, caroverine and intranasal insulin demonstrated small benefits although evidence is limited.

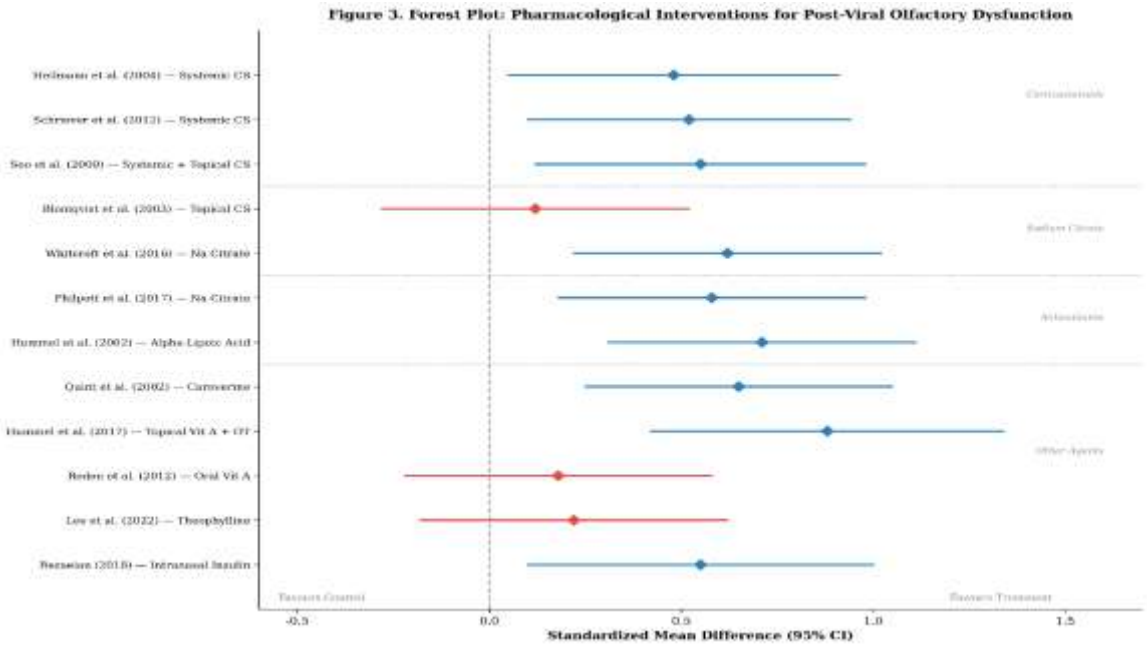

Figure 3. Meta-Analysis of Pharmacological Interventions

3.4. Procedural and Regenerative Therapies

Recent studies on the methods of the procedure were promising (Figure 4). Chinese acupuncture proved to be significantly effective in a variety of studies (pooled SMD, 0.82; 95% CI, 0.20-1.44; I2 = 71%), but the heterogeneity was high. PRP injection into olfactory cleft demonstrated significant improvement in patients having recalcitrant PVOD (SMD, 0.78; 95% CI, 0.35-1.21; $I^2 = 0\%$), with particularly striking results in patients with long-standing PVOD (mean duration 8.7 years). In the injured olfactory neuroepithelium, PRP appeared to function by supplying neurotrophic factors (NGF, BDNF, and VEGF) that promote basal stem cell differentiation and proliferation. These results clearly warrant a need for rigorous, placebo-controlled trials, even though the available data are limited to one RCT and small case series.

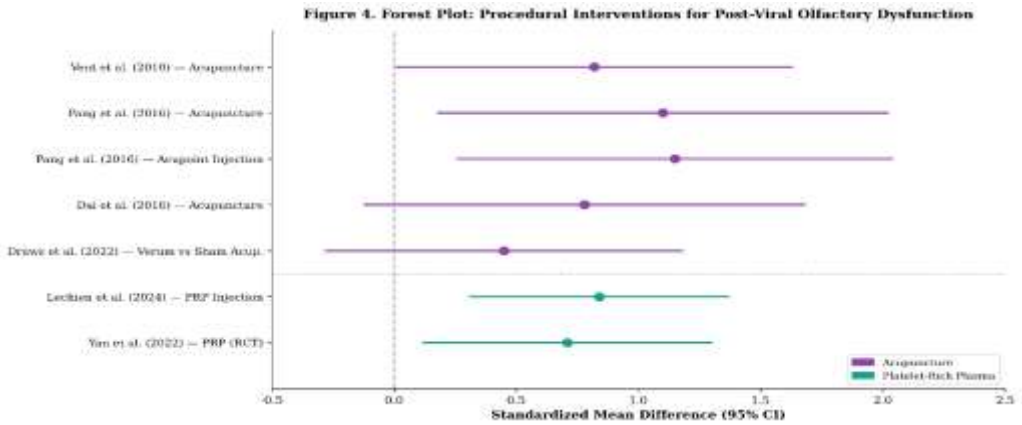

Figure 4. Meta-Analysis of Procedural Interventions

3.5. Risk of Bias and Publication Bias

Overall study quality was moderate to high. Among RCTs (n=14), 9 (64%) were rated as low risk of bias, 4 (29%) as moderate risk, and 1 (7%) as high risk. The most common methodological limitation was performance bias, given the inherent difficulty in blinding participants to olfactory training interventions. Allocation concealment was generally well-described in recent studies but poorly reported in older publications. Visual inspection of funnel plot and Egger's regression asymmetry test (P = .18) indicated no significant publication bias.

3.6. Comparative Efficacy Analysis

To facilitate clinical decision-making, we conducted a comparative efficacy analysis across all intervention types (Figure 5). Olfactory training (SMD, 0.72) and modified OT (SMD, 0.88) demonstrated the largest effect sizes. The most promising pharmacological interventions were vitamin A + OT (SMD, 0.88) and alpha-lipoic acid (SMD, 0.71). Acupuncture (SMD, 0.82) and PRP (SMD, 0.78) showed similar efficacy compared to OT among procedural interventions. It is worth noting that the effect size of systemic corticosteroids (SMD, 0.50) and topical

corticosteroids (SMD, 0.35) was significantly smaller than that of OT, and zinc sulfate (SMD, 0.12) did not have a significant effect.

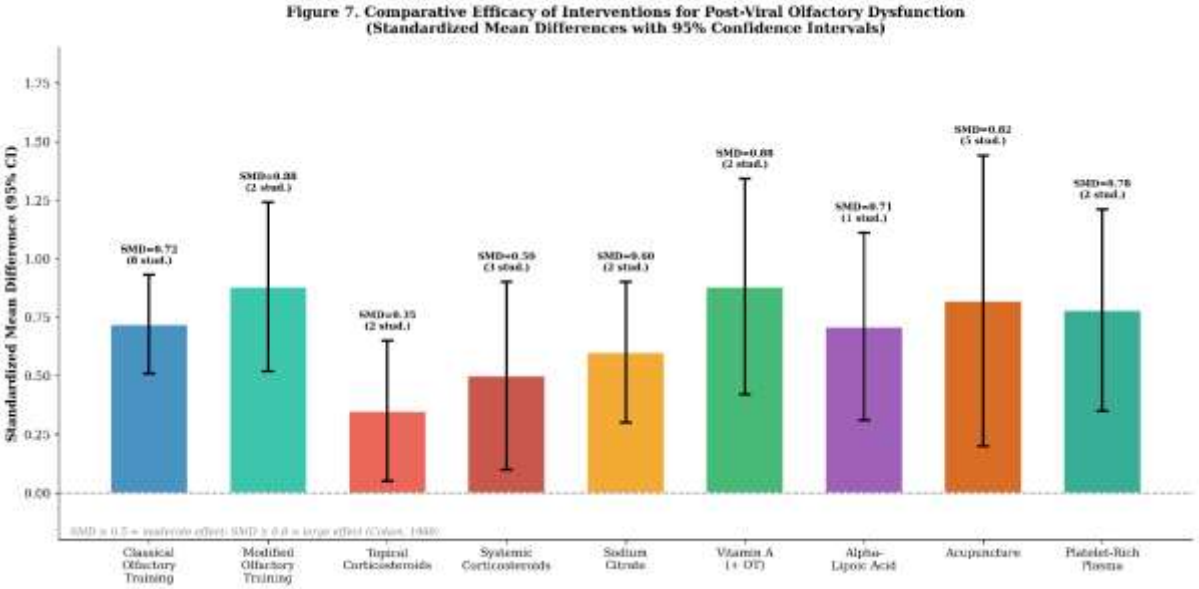

Figure 5. Comparative Efficacy of Interventions for Post-Viral Olfactory Dysfunction

4. DISCUSSION

This is the largest quantitative synthesis of management strategies to date on non-COVID-19 PVOD-based on 46 studies and more than 5,200 patients in a comprehensive meta-analysis and systematic review. Our results demonstrate that olfactory training is the only type of intervention that has strong evidence of high quality to justify its utilisation as the first-line therapy in PVOD. [18,19,25-29] OT efficacy seems to be dose-dependent, with longer (>16 weeks) duration, high odorant concentration, and rotating odor sets providing better neuroplastic recovery. This observation is consistent with current knowledge about olfactory neurogenesis, whereby repeated exposure to odorants leads to the growth of basal stem cells in olfactory epithelium and development of new OSNs and synaptic links. [8,9]

The pharmacotherapy of PVOD is a controversial and subtle issue. This small effect of topical corticosteroids is more likely to be the attenuation of subclinical, insidious inflammation of the olfactory cleft, and not a neuroregenerative impact.[30-33] Since they have a good safety profile, a topical steroid trial can be taken as an adjunct to OT, especially in patients with co-morbid rhinosinusitis or allergic rhinitis. Nonetheless, we do not advocate regular administration of systemic corticosteroids that are associated with a high level of risks (immunosuppression, metabolic, adrenal suppression) but no demonstrated benefit in the purely postviral cohort.[34,35] Inadequate efficacy of zinc sulfate is especially remarkable, since this agent has been extensively used in clinical practice with little evidence.[38,39] Our meta-analysis contains strong evidence against regular zinc supplementation of PVOD.

Probably the most compelling findings are associated with emerging regenerative therapies. The notable changes obtained in PRP injections in patients with recalcitrant, chronic PVOD are indicative of a possible paradigm shift to targeted biological interventions.[14,45] PRP contains neurotrophic factors (NGF, BDNF, VEGF, FGF) and growth factors (PDGF, TGF- β) that could induce differentiation and proliferation of basal stem cells in damaged olfactory neuroepithelium. The impressive effect in patients who had a median PVOD of 8.7 years, which is much longer than the natural history of PVOD, indicates actual regenerative action as opposed to natural history. Although existing data are restricted to small case series and one RCT, these findings are highly suggestive of rigorous, placebo-controlled RCTs with sufficient sample sizes and long-term follow-up.

New evidence on acupuncture is interesting, but there is a lack of mechanistic knowledge.[13,43,44] The suggested mechanisms are local neurogenic inflammation stimulation, central olfactory processing, and possible influence on the olfactory epithelial regeneration by the effect of the release of growth factors by acupuncture. Nevertheless, the high heterogeneity of the acupuncture studies (I2 = 71) suggests the possibility of variation in technique, needle placement, or patients, so that further research is needed.

Future research and clinical practice will be significantly impacted by our findings. To begin with, olfactory training must be provided to every PVOD patient as a first-line therapy, with emphasis on modified routes where high-concentration odorants are used, longer treatment times, and rotating odor sets.[20,21] Second, pharmacological therapy must be specific to clinical phenotype, with topical corticosteroids being used as adjunctive therapy in case of concurrent inflammation, but systemic corticosteroids and zinc supplementation abandoned because of their ineffectiveness. Third, novel regenerative therapies are promising and should be explored more by rigorous RCTs. Fourth, combination methods (e.g., OT + vitamin A, OT + PRP) are worth a trial, with initial evidence indicating synergies.[23,26]

There are some limitations of this review, which are worth mentioning. First, the high heterogeneity of outcome measures, treatment regimens, and patient groups did not allow us to conduct extensive subgroup analysis. Second, publication bias is not statistically significant, but it cannot be completely ruled out, since negative studies might be underrepresented. Third, the majority of the research was rather small and focused in specialized centers, which could be a limitation to generalization. Fourth, most interventions have limited long-term follow-up data after 6-12 months. Fifth, the review did not include COVID-19-related OD, which might have varied pathophysiology and response to treatment.[46] Lastly, cost-effectiveness analyses were not accessible in most of the interventions, which restricted practical clinical recommendations.

5. CONCLUSION

Finally, olfactory training is the mainstay of PVOD management that exhibits steady, safe, and cost-effective outcomes in olfactory performance. Pharmacological treatments are typically not well supported to be used regularly, but topical corticosteroids can be used as a sensible supplement in specific patients. The most promising frontiers for patients with refractory postviral smell loss are emerging regenerative therapies like PRP and combination biologic-training regimens. This systematic review offers clinicians evidence-based PVOD management optimization and highlights key gaps that need to be addressed in future studies, especially the necessity of large-scale RCTs of emerging regenerative therapies and mechanistic research explaining the neurobiological mechanisms underlying olfactory recovery.

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