Therapeutic options of post-COVID-19 related olfactory dysfunction: a systematic review and meta-analysis*

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Abstract

Background: Olfactory dysfunction is a typical post-COVID-19 presentation, affecting patients' quality of life. There are currently multiple treatment options in this group of patients such as oral and intranasal corticosteroids, olfactory training, oral vitamin-mineral supplementation, amongst others. This meta-analysis aims to consolidate existing evidence for current therapies in patients with persistent olfactory dysfunction related to COVID-19 infection and evaluate the possible role of corticosteroid add-on therapy in olfactory training.

Methodology: A systematic review and meta-analysis to study current treatments/interventions for olfactory dysfunction in post-COVID-19 infection were conducted. Data were pooled for the meta-analysis. The outcomes include subjective or objective olfactory assessment major and minor adverse reactions.

Results: Eleven studies (1414 participants) were included in this review, with six studies (916 participants) then assessed for the meta-analysis. Combined treatment of intranasal corticosteroid (INCS) with olfactory training (OT) has no benefit over OT monotherapy from both a VAS score improvement and identification component of Sniffin' Sticks test standpoint. In addition, there were no differences in improvement of TDI score between combined oral corticosteroid (OCS) with OT therapy compared to OT alone. Olfactory function was, however, significantly improved after OT.

Conclusion: There were no significant differences in the improvement of olfactory scores in combination INCS+OT or OCS+OT therapies compared to OT monotherapy. However, there is improvement in olfactory function after OT.

Key words: olfactory dysfunction, COVID-19, SARS-CoV-2, corticosteroids, olfactory training, smell

Introduction

The outbreak of SARS-CoV-2 was first announced by the World Health Organization (WHO) in December 2019. Up till now, there are over 300 million confirmed cases of SARS-CoV-2 infection worldwide [(1)]. New onset loss of smell and taste is one of the major symptoms in these patients [(2)]. However, most of the patients' sense of smell gradually returned to normal. When monitoring patients with COVID-19-related anosmia, approximately 40-50% of patients recovered their sense of smell within 14 days and improvement in olfactory function was significant at their two-month follow-up [(3,4)]. Studies indicate that 30-43% of patients get their sense of smell back in 2-3 months; nevertheless,10-15% of patients experience a six-month olfactory loss despite full recovery from the infection and no detectable virus in the respiratory system [(5-7)]. Olfactory dysfunction has substantial impact on patients' quality of life, including social anxiety, decreased appetite and depression. Loss of smell also results in occupational impairment and safety. Therefore, treatment should be considered for patients with symptoms of olfactory impairment beyond two weeks [(8,9)]. Although the pathophysiology of post-COVID-19 olfactory dysfunction has not been well-established, many etiologies have been proposed. A combination of multi-

level damage to the olfactory pathway is believed to be involved in this process [10,11]. The impairment of odorant signal transduction by ACE2 [12,13], persistent inflammatory reaction [14], transient neuropraxia, and damage of olfactory neuroepithelium caused directly by the virus and excessive cytokine production lead to sensorineural olfactory loss. Other proposed etiology includes conductive loss due to an inflammatory reaction of the nasal mucosa – which subsequently induces local mucosal tissue edema [15]. Currently, there is still no consensus guideline on the management of post-COVID-19 olfactory loss. Most treatments are similar to the treatment of post-viral olfactory dysfunction (PVOD), including oral corticosteroids (OCS), topical corticosteroids, zinc, vitamin A, and non-pharmacologic therapy such as olfactory training (OT) [8,16-18]. Based on current evidence [19,20], OT is the only treatment with significant improvement in PVOD and post-COVID-19 olfactory dysfunction.

Two observational studies demonstrated olfactory impairment improvement in post-COVID-19 patients after 4-8 weeks of OT [21,22]. In post-COVID-19 related olfactory dysfunction, topical intranasal corticosteroids (INCS) may not play a significant role in the improvement of smell [23,24]. Patients who received combined INCS+OT therapy also reported improvement in smell scores. However, when compared to the OT monotherapy treatment group, there was no benefit of add-on INCS [25-27]. Other studies show improvement of olfactory function in post-COVID-19 patients who received a short course of OCS combined with OT [27,28]. Thus, the current treatment for olfactory dysfunction from COVID-19 infection is still debated. Even though many mechanisms leading to olfactory dysfunction after SARS-CoV-2 infection have been proposed and many treatment options have been studied, the efficiency of the proposed methods has not clearly been identified. Different treatments or a combination of multiple therapies may be an option for patients, but the side effect profile should also be a major concern. This systematic review aims to assess the current treatment options for olfactory loss lasting more than two weeks in previously infected- SARS-CoV-2 patients. The benefits and effects of add-on corticosteroids, either via oral or intranasal routes, in combination with OT or OT monotherapy alone in relieving symptoms of smell impairment after SARS-CoV-2 infected patients are also assessed.

Materials and methods

Eligibility criteria

We adhered to the PRISMA 2020 guidelines for reporting systematic reviews [29]. Study designs included were randomized controlled trials, case-controlled studies, cohort studies, case series and pre-print papers reporting any treatments/interventions of any duration in adult patients (≥18 years old) with post-COVID-19 olfactory dysfunction. Treatments may consist of intranasal steroid sprays, intranasal steroid drops/rinses, systemic steroids, OT, zinc, intranasal vitamin A, omega 3, alpha lipoic acid, other vitamins, nutritional supplements or a combination of any of the above. Patients had a confirmed history of COVID-19 infection with either RT-PCR or immunological testing. The outcomes were either subjective olfactory assessment (Visual Analog Score, Self-Rating Olfactory Score or the Sino-Nasal Outcome Test (SNOT-22)) or objective olfactory assessment such as TDI scores (odor threshold (T), discrimination (D), or identification (I)), University of Pennsylvania Smell Identification Test (UPSIT), etc., major and minor adverse reactions. Articles not published in English, review articles, case studies, and case reports were excluded. Patients that may be suffering from olfactory dysfunction due to other conditions such as a previous history of head trauma, history of anosmia before the COVID-19 pandemic, severe sinonasal diseases, and previous sinonasal surgery were excluded from this study.

Information sources and search strategy

Electronic systematic and manual searches for any study designs were conducted since January 1, 2020, with no publication status restrictions. The last searched date was March 31, 2022. In addition, an electronic literature search was performed using SCOPUS, MEDLINE, The Cochrane Library, World Health Organization (WHO) COVID-19' Global literature on coronavirus disease database and manual literature search.

Study selection process

The data were extracted manually by two independent reviewers. Title and abstract screening based on eligibility criteria was performed, and then full-text articles of the selected studies were reviewed.

Data extraction

Two authors (VA and JS) extracted the data and details of the studies. Any contradictions such as insufficient information or conflicting data found during the data collection process were resolved by the third author (JK).

For all included trials, collected data included:

1. Trial details: publication details, study design, methodological criteria
2. Participant characteristics: mean age, gender, inclusion, and exclusion criteria
3. Treatment details: types of regimen, dosage, frequency, mode of administration, duration of follow up, withdrawal (if available data)
4. Outcome details: The primary outcomes were subjective olfactory assessment or objective olfactory assessment and major or severe adverse reactions from the intervention. The subjective olfactory assessment is a self-reported olfactory function such as the Visual Analog Score, Self-Rating Olfactory Score or the Sino-Nasal Outcome Test (SNOT-22). The objective olfactory assessment can be performed using psychophysical testing, for

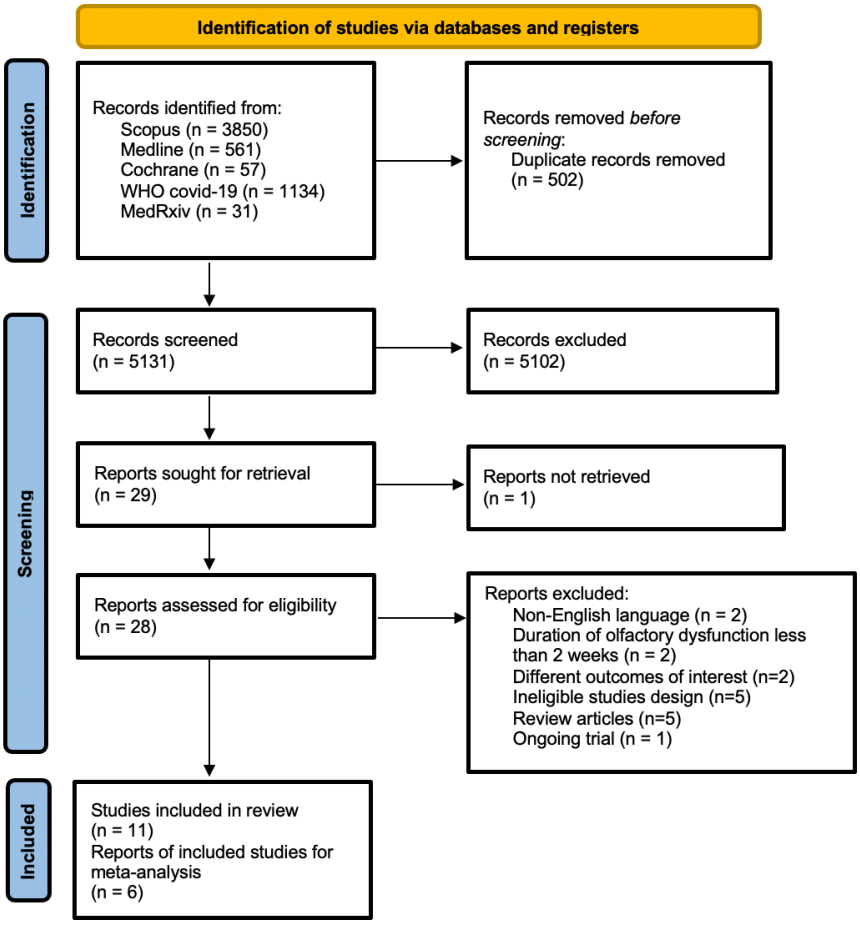

Figure 1. PRISMA 2020 flow diagram of study selection for systematic review and meta-analysis.

example, odor threshold (T), discrimination (D), or identification (I) (TDI) scores. Two commonly available tests are the Sniffin' Sticks and the UPSIT. Secondary outcomes were any minor side effects from the intervention.

Risk of bias in included studies

The risk of bias in the included studies was assessed by two independent reviewers, guided by the Cochrane revised tool to determine the risk of bias in randomized trials (RoB 2) for randomized studies [30]. The tool assesses the risk of bias and applicability of the study to the review question in six domains: the randomization process, deviations from the intended interventions, missing outcome data, outcome measurement, selective outcome reporting and overall risk of bias. Based on answers to the questions, judgment for each bias domain and for overall risk of bias, can be 'Low risk', 'Some concerns', or 'High risk' risk of bias. For non-randomized studies, the NEWCASTLE - OTTAWA quality assessment scale was used to assess the risk of bias [31]. JBI's critical appraisal tools was used to assess the risk of bias for cross-sectional descriptive studies and case series [32-34]. Disagreements were resolved through by consultation with the third reviewer.

Data synthesis and statistical analysis

We utilized an odds ratio and 95% confidence interval (CI) for dichotomous data, Mean Differences (MD) and 95% CI for continuous data. We assessed heterogeneity among included studies by calculating I^2. An I^2 value of less than 30% was defined as low heterogeneity, between 30-70% defined as moderate heterogeneity, and greater than 70% defined as substantial heterogeneity. With low statistical heterogeneity, the fixed-effect model was used. When statistical heterogeneity was high, the random effect model was used. The data were synthesized for meta-analysis using Review Manager (RevMan) version 5.4.1.

Results

Study selection and study characteristics

5131 articles were identified and initially reviewed after exclusion of duplicates; all studies were from electronic searches and no additional studies were found from manual searching. Of these, 28 studies were included after title and abstract screening. After full-text review, 17 studies were excluded due

to non-English language, duration of olfactory dysfunction less than two weeks, different outcomes of interest, ineligible study design, review articles and ongoing studies. 11 studies were finally included for the systematic review [22-28,35-38], and 6 studies were included for the meta-analysis [22,25-28,35] (Figure 1). Among included studies, 7 were randomized controlled studies, 2 were case-controlled, 1 was observational study and 1 was case series. One study evaluated the effects of INCS combined with OCS, 2 studies evaluated topical nasal corticosteroids, 2 studies evaluated INCS+OT compared with OT monotherapy, 1 study evaluated OCS+OT compared with OT monotherapy, 1 study randomized patients into 3 groups comparing INCS+OT, OCS+OT, and OT monotherapy, 2 study evaluated OT, and 2 study evaluated other interventions. Table 1 shows the characteristics of included studies.

Participants

The 11 included studies amounted to a total of 1414 participants. 38% were male and 62% were female. Mean participant age ranged from 18 to 84 years old. Previously infection with the SARS-CoV-2virus was confirmed by RT-PCR test or immunological testing (IgM/IgG for SARS-CoV-2).

Intervention

One randomized controlled trial (RCT) used a combined oral prednisolone treatment starting with 1 mg/kg/day and then tapering the dose for 15 days, followed by betamethasone nasal irrigation for 15 days, ambroxol (a mucolytic) and rinazine (a decongestant) for 15 days. One RCT used 0.055% Triamcinolone Acetonide nasal spray 440 mcg/day (55 mcg per puff, two puffs into each nostril twice daily) combined with hypertonic NSS irrigation 10 cc per nose, twice daily. This study also used hypertonic NSS irrigation 10 cc per nose, twice a day for one months in another study group. In addition, one RCT used intranasal betamethasone sodium phosphate drops (0.1 mg/ml) 3 drops for each nostril 3 times daily until smell function recovered with the maximum duration of 1 month. In the group comparing INCS+OT to OT, two studies used Mometasone Furoate nasal spray 200 mcg/day (50 mcg per puff, two puffs into each nostril once daily). One study also used Mometasone Furoate nasal spray but with a higher dose of 400 mcg/day (2 puffs into each nostril twice daily). The duration of topical corticosteroid usage ranged from 15 days to 1 month. For combined treatment of systemic corticosteroids with OT, two studies used oral methylprednisolone with the dosage of 32 mg/day (equivalent to prednisolone 40 mg/day) for 10 days and 0.5 mg/kg/day (equal to prednisolone 0.625 mg/kg/day) for 10 days respectively. OT duration ranged from three weeks to sixteen weeks. One randomized controlled study used daily oral mineral supplement that contained Palmitoylethanolamide (PEA) 700 mg and Luteolin 70 mg add on to OT for 30 days. One study used intranasal delivery of insulin fast-dissolving film which contains 100 IU insulin per film applied into the patient's olfactory cleft by 30-degree nasal endoscopy. The intervention took twice per week for four weeks (8 visits). One case series used intranasal photobiomodulation therapy (PBMT) using either Therapy EC® (DMC, Sao Carlos, SP, Brazil) or Laser DUO® (MM Optics Ltda Sao Carlos, SP, Brazil) at 660 nm, on contact mode, with 100 mW of power, and 18 J of energy on the nasal mucosa, corresponding to 3 min of irradiation per nostril. The PBMT protocols were divided into three groups. Group 1 composed of 10 laser sessions, twice a week and with a 48-hour interval. Group 2 composed of 5 laser sessions, twice a week with a 48-hour interval. Group 3 composed of 10 laser sessions, with a 24-hour interval. The details of the interventions are described in Table1.

Outcomes

OCS, Topical steroids

One randomized, double-blind, placebo-controlled clinical trial reported that betamethasone drops has no significant effect on the recovery time of anosmia compared to placebo (Hazard ratio 0.88, 95% CI 0.68-1.14; p=0.31) [23].

One multicenter randomized controlled study assessed the effects of systemic prednisolone and nasal irrigation with betamethasone, ambroxol and rinazine for 15 days [37]. The study revealed significant improvement in olfactory performance score (CCCRC score) in the treatment group compared to the control group at 20-day (median olfactory score of 40 (IQR 45) vs 10 (IQR 15); p=0.011) and 40-day (60 (IQR 40) vs 30 (IQR 25); p=0.024) evaluations.

One RCT used Self-Rating Olfactory Score (SROS) and Olfactory Dysfunction Duration (ODD) to compare the effect of nasal saline irrigation with Triamcinolone Acetonide versus nasal saline irrigation alone [24]. The study revealed that the group receiving NSS + Triamcinolone Acetonide treatment had a significantly higher SROS score than the control group which were not given any treatment (p=0.018) and the group given saline irrigation alone (p=0.033). The Olfactory Dysfunction Duration were shortest in the group with topical triamcinolone treatment compare to the group that received nasal saline irrigation alone (mean ± SD, 5.6 ± 3.2 vs 12.1 ± 2.2; p = 0.028) and no treatment group (mean ± SD, 5.6 ± 3.2 vs 15.2 ± 2.3; p = 0.022).

INCS+OT vs OT

Two randomized studies used the visual analog score (VAS) to assess improvements in olfactory outcomes. The VAS smell score was subjectively assigned by patients from 0-10, where 0 indicates complete loss of smell and 10 indicates normal olfactory sensation. One study used the identification component of the Sniffin' Sticks test to assess the olfactory outcomes. The Sniffin' Sticks test is an objective test used to evaluate olfactory performance. It is composed of three tests, including odor

Table 1. Characteristics of included studies.

First Author	Year	Study type	Patients age (years old)	Number of patients (M/F)	Intervention	Control
Abdelalim [25]	2021	Prospective RCT	18-61	100 (46/54)	Mometasone Furoate nasal spray 2 puff(100mcg)/nostril once daily 3 weeks + OT 3 weeks	OT 3 weeks
D'Ascanio [35]	2021	Randomized-controlled pilot study	28-56	12 (4/8)	Olfactory training/stimulation 30 days + daily treatment with PEA 700mg/Luteolin oral supplement 70 mg for 30 days	OT 30 days
Denis [22]	2021	Observational study	18-84	548 (189/359)	OT and visual stimulation	OT 4 weeks
Kasiri [26]	2021	Prospective randomized double blind clinical trial	26-44	77 (39/38)	Mometasone Furoate nasal spray 2 puff(100mcg)/nostril twice daily 4 weeks + OT 4 weeks	Topical 0.9% saline spray 2 puff/ nostril twice daily 4 weeks + OT 4 weeks
LeBon [28]	2021	Case control	28-58	27 (6/21)	32 g of methylprednisolone once daily 10 days + OT 10 weeks	OT 10 weeks
Mohamad [36]	2021	Single-blinded randomised parallel design	18-70	40 (21/19)	Insulin fast-dissolving film (100 units) twice weekly 4 weeks	Placebo 4 weeks
Rashid [23]	2021	Randomised, double-blind, placebo-controlled clinical trial	23-38	276 (78/198)	Intranasal betamethasone sodium phosphate drops (0.1 mg/ mL) 3 drops for each nasal cavity 3-times daily until recovery with maximum of 1 month	0.9% NaCl intravenous solution placebo drops
Saussez [27]	2021	Prospective observational controlled study	25-57	152 (62/90)	- Methylprednisolone 0.5 mg/kg/day 10 days + OT 2 months - Mometasone Furoate nasal spray 2 puff(100mcg)/nostril once daily 1 month + OT 2 months	OT 2 months
Soares [38]	2021	Case series	20-59	14 (2/12)	Intranasal PBMT Therapy EC® (DMC, Sao ˜ Carlos, SP, Brazil) or Laser DUO® (MM Optics Ltda Sao ˜ Carlos, SP, Brazil) at 660 nm, on contact mode, with 100 mW of power, and 18 J of energy on the nasal mucosa, corresponding to 3 min of irradiation per nostril The PBMT protocols were as follows: Group (1) 10 laser sessions, twice a week and with a 48-hour interval Group (2) 5 laser sessions, twice a week and with a 48-hour interval Group (3) 10 laser sessions, with a 24-hour interval.	-
Vaira [37]	2021	Multicenter prospective randomized case-control study	27-57	18 (7/11)	prednisolone 1 mg/ kg/day and tapering the dose for 15 days and nasal irrigation with betamethasone, ambroxol, a mucolytic, and rinazine, a decongestant, for 15 days.	No treatment
Yildiz [24]	2021	Single-center randomized-controlled study	18-61	150 (84/66)	Group 1: no treatment Group 2: hypertonic NSS irrigation saline irrigation (hypertonic solution/10 cc per nose, twice a day/1 month) Group 3: hypertonic NSS irrigation 10 cc per nose, twice a day + 0.055% TA nasal spray 2 puff/nostril twice daily	No treatment

RCT = Randomized Controlled Trial; OT = Olfactory Training; PEA = Palmitoylethanolamide; PBMT = Photobiomodulation Therapy; NSS = Normal Saline Solution; TA = Triamcinolone Acetonide.

threshold(T), odor discrimination(D), and odor identification(I). The identification test is comprised of 16 pens (16 common odorants). Each pen is presented once over an interval of at least 30 seconds then the subjects chose the smell between four

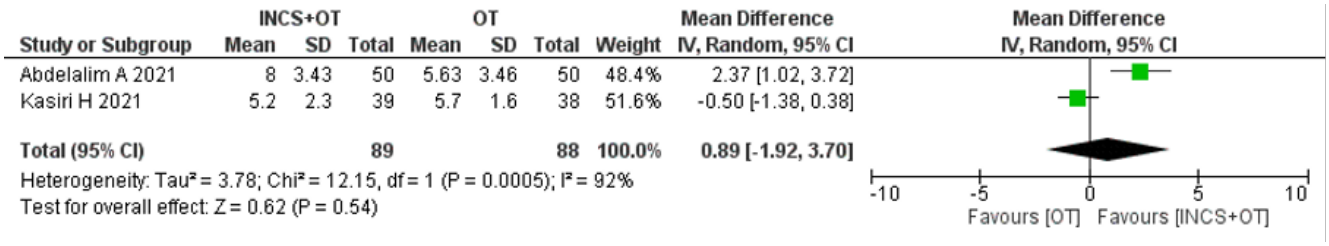

Figure 2. Improvement of VAS score: Intranasal corticosteroid plus olfactory training vs olfactory training monotherapy.

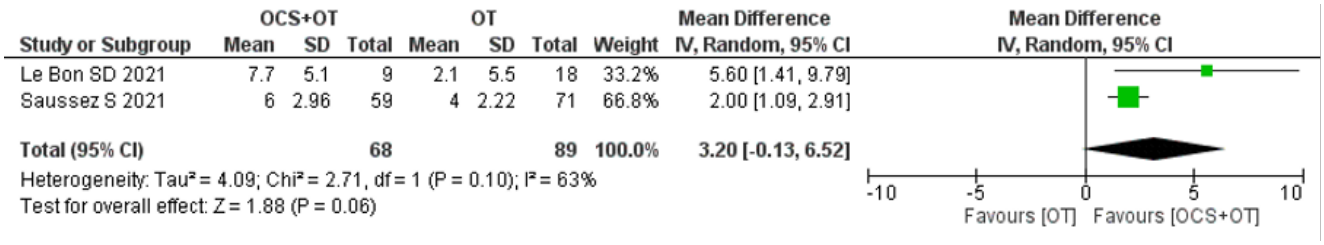

Figure 3. Improvement of TDI score: Oral corticosteroid plus olfactory training vs olfactory training monotherapy at one month.

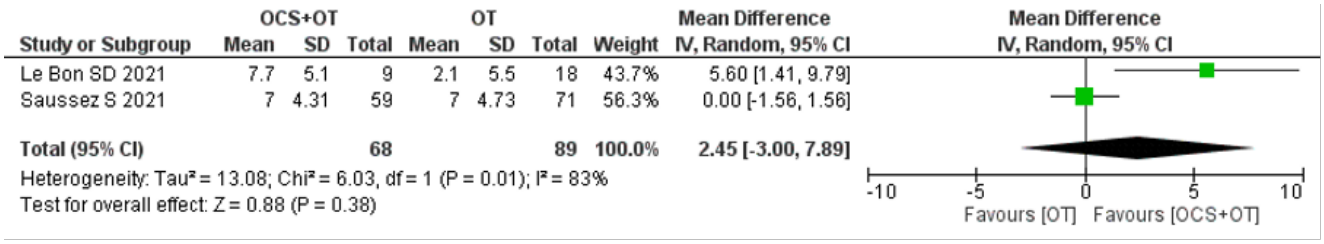

Figure 4. Improvement of TDI score: Oral corticosteroid plus olfactory training vs olfactory training monotherapy for a two-month period.

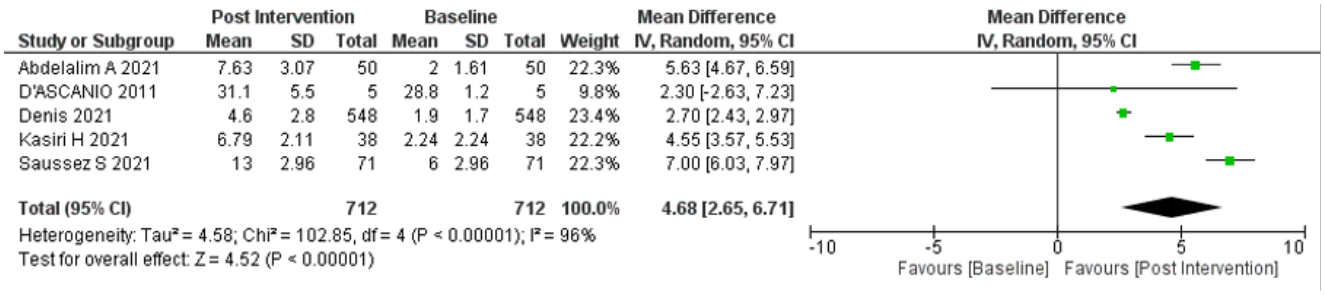

Figure 5. Improvement of olfactory function: Pre- vs Post-olfactory training.

given choices [39,40]. The final score ranges from 0 (none correctly identified) to 16 (all correctly identified). According to the study, a score of 0-8, 9-11, 12-16 represents anosmia, hyposmia and normosmia, respectively [27,41,42]. There was no significant difference in the VAS score between the INCS+OT and OT monotherapy groups (MD 0.89, 95%CI -1.92 to 3.7, p=0.54, 2 RCTs) [25,26]. An I2 of 92 indicated substantial heterogeneity in the two RCTs [25,26]. There was also no significant statistical difference in the identification component of the Sniffin' Sticks test between the INCS+OT and OT groups at both one and two months (MD 2, 95%CI -0.66 to 4.66, p=0.139 at one month, MD -1, 95%CI -2.83 to 0.83, p=0.281 at two months, 1 case-controlled study) [27]. This is shown in Figure 2.

OCS+OT vs OT

The Sniffin' Sticks test was used to assess olfactory function in two studies. One of them only evaluated the identification component [27]. The other calculated the sum of three subsets of the test. When TDI ≥30.75 and <30.75, the patients were defined as having normosmia and dysosmia, respectively [28]. There was no statistical difference in the smell score from the Sniffin' Sticks test between the OCS+OT and OT groups at the one (Figure 3) and two-month period (Figure 4); (MD 3.2, 95%CI -0.13 to 6.52, p=0.06 at one month, MD 2.45, 95%CI -3 to 7.89, p=0.38 at two months in 2 case-controlled studies)[27,28]. An I^2 of 63% and 83% represent moderate and substantial heterogeneity.

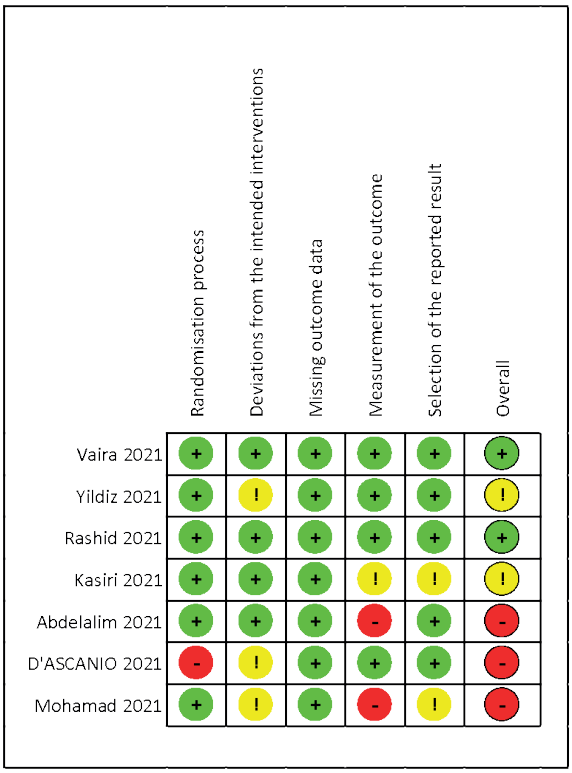

Figure 6. Risk of bias summary for RCT: each risk of bias item for each included study.

Olfactory training

Six studies reported improvement in olfactory outcomes after OT. At baseline, VAS, identification component of Sniffin' Sticks test and TDI score were considered low (anosmia or dysosmia) in all six studies [22,25-28,35]. One study was excluded from our meta-analysis due to incomplete data for analysis [28]. Therefore, five studies were included for final meta-analysis [22,25-27,35]. The results showed statistically significant improvement in the smell score after OT (Figure 5; MD 4.68, 95%CI 2.65-6.71, p<0.00001) [22,25-28,35].

Oral supplementation

One randomized study assessed improvement of olfactory function score between OT+PEA/Luteolin oral supplement and OT alone [35]. The treatment group (OT+PEA/Luteolin oral supplement) showed statistically significant improvement in TDI score compared to control group (OT) (MD 2 for control group, 4 for treatment group; KW: p=0.01).

Intranasal Insulin fast-dissolving film

The result from one single-blinded randomized parallel design [36] showed that the insulin-loaded fast-dissolving film had a statistically significant increase in the olfactory detection scores (mean ± SD of 7.9 ± 1.2) and olfactory discrimination values (6.7 ± 0.5) compared to placebo group (3 ± 0.8, 2.8 ± 1 respectively).

Intranasal Photobiomodulation Therapy (PBMT)

One case series reported improvements in smell loss in all three groups of patients after received a treatment of intranasal PBMT [38]. In group 1 (10 laser sessions, twice weekly, 48-hour interval) reported an average improvement of visual analog scale (VAS) score of 4.4. In group 2 (5 laser sessions, twice weekly, 48-hour interval) reported an average improvement of visual analog scale (VAS) score of 4.8. The highest smell improvement was observed in group 3 (10 laser sessions daily, 24-hour interval) with a visual analog scale (VAS) score of 7.67.

Adverse events

Four studies mentioned adverse events related to the intervention [26-28,37]. Two studies reported that there was no side effect related to the therapy [26,37]. A study from LeBon and Saussez reported minor side effects of OCS treatment, including mainly insomnia, headache, and abdominal discomfort [27,28]. The most common reported side effects were insomnia. None of the studies reported any major adverse effects. No side effects related to OT were reported.

Risk of bias in the included studies

Of the included RCTs, 86% had a low risk of bias in the randomization process. However, 43% had some concern for bias in the blinding of outcome assessment. All studies had a low risk of bias in missing outcome data. Fifty-seven percent had a low risk of bias in the outcome measurement, while 29% had some concern for bias in selective outcome reporting (Figure 6). For non-randomized studies, the mean quality score of the studies was 6.5 with a range of 6-7 when evaluated by the Newcastle-Ottawa Scale (NOS) and a score of 5 and 6 when evaluated by JBI's critical appraisal tools for analytical cross sectional studies and case series respectively (Figures 7 and 8).

Discussion

It has been more than 3 years since the COVID-19 outbreak. The virus has changed our lives globally as well as affecting the world economy. So far, hundreds of variations have been detected, and various symptoms vary from mild to severe. COVID-19 patients may have recovered from the illness but long-term effects may be present – one of which is olfactory dysfunction. The current management of post- SARS-CoV-2 infection related olfactory disorder is still controversial since the pathogenesis is complex and the actual mechanism is still unknown. Many treatment options and interventions have been widely proposed to reduce symptoms and improve quality of life. Our systematic review and meta-analysis revealed that either treatment with INCS, OCS, OT or the combination of these is beneficial in improving the olfactory score in patients with post-COVID-19 olfactory impairment when compared to pre-treatment baseline scores. A short course of OCS+OT compared to OT monotherapy

Non-RCT studies	Selection	Comparability	Outcomes	Total stars
Saussez S (2021)	✷✷✷	✷✷	✷✷	7
LeBon SD (2021)	✷✷	✷✷✷	✷	6

Figure 7. Risk of bias assessment, the NEWCASTLE - OTTAWA quality assessment scale for non-RCT studies.

Studies	Design	Score based on appropriate JBI appraisal*										Overall
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	
Denis 2021	Observational studies	Y	Y	Y	Y	N	N	U	Y	NA	NA	5/8
Soares 2021	Case series	Y	Y	Y	U	U	Y	N	Y	N	Y	6/10

Figure 8. Risk of bias assessment, JBI's critical appraisal tools check list. *Maximum score, appropriate appraisal for either cross-sectional study or case series was used, cross-sectional study – 8 criteria, case series – 10 criteria. Y=Yes; U=Unclear; N=No; NA= Not Applicable.

alone has the most benefit in shortening the duration of olfactory loss and improving the olfactory score with no major side effects. However, when the meta-analysis completed, the results showed that combined INCS+OT or OCS+OT was not superior to OT monotherapy. This supports the theory that SARS-CoV-2 induced olfactory loss by damaging the sustentacular cells via ACE2 receptors, which is by far the most likely mechanism. OT is another non-pharmacological treatment for olfactory loss. The evidence revealed that OT improves smell function through neural rearrangement and initiates neural reorganization mechanism. Systematic review and meta-analysis from Kattar et al. reported a very strong improvement in post-viral olfactory dysfunction with OT [20]. The more the patient compliance and adherence, the more effective OT. According to our study, patients with post-COVID-19 related olfactory loss also show significant improvement after OT. A study from Denis et al. also showed more improvement with a longer duration of OT [21]. Other interventions proposed to treat the COVID-19 induced olfactory dysfunction including PEA/Luteolin oral supplement, intranasal insulin fast-dissolving film and intranasal photobiomodulation which the results also showed improvements of the smell function [35,36,38]. Palmitoylethanolamide (PEA), classified as a dietary supplement, is an endogenous fatty acid amide claimed as one of the treatments for COVID-19 infection due to its anti-inflammatory and neuroprotective effects [43]. However, with the limited data, well-designed studies and safety margins, further studies are required and we cannot recommend or advised against these treatments.

Nevertheless, it should be kept in mind that the results of the pre- and post-treatment groups may have some biased outcomes. And also the lack of a control group to assess the effect of OT alone is one reason why we cannot conclude that the improvement of olfactory function was due to the intervention rather than the course of the disease itself. Regardless, based on our results, the improvement of the clinical and the smell score and the lack of any adverse side effects, we propose that OT should be the primary treatment in patients with persistent post-COVID-19 olfactory loss. No benefit of add-on INCS or OCS was observed in our study.

The main limitations of this study were short follow-up periods, a small number of well-designed studies and lack of the control group to assess the true effects of OT on the smell function in the COVID-19 patients. Another limitation of our study was the quality and heterogeneity of the included studies. One of the foremost biases was allocation concealment and blinding. Moreover, some studies used subjective outcome measurements with participants arbitrarily assigning scores themselves. Therefore, the scoring might be variable. Randomized-controlled trials with objective outcome measurements should be conducted as potential future work.

Conclusion

Based on evidence from these studies, all of the included interventions had the positive effects on the smell function. However, neither INCS+OT nor OCS+OT improved olfactory outcomes when compared to OT alone in patients with post-COVID-19 related olfactory loss. Therefore, OT is considerable the most recommended management in patients with post-viral olfactory

dysfunction, including post-COVID 19 related olfactory loss.

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None

Authorship contribution

VA: study design, search, study selection, data collection, data analysis, drafting the articles, and final approval of the version to be published; JS: search, study selection, and final approval of the version to be published; SA: Final approval of the version to be published; KSn: Final approval of the version to be published; SC: Final approval of the version to be published; KSe: Final approval of the version to be published. JK: conception, study design, search, study selection, data analysis, drafting the articles, Critical revision of the article, and final approval of the version to be published.

Conflict of interest

The authors have declared no conflict of interests.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Search terms.

Scopus	(ALL("Olfactory dysfunction") OR ALL("Olfactory disorders") OR ALL("Olfactory loss") OR ("smell dysfunction") OR ("smell loss") OR ("smell disorders") OR ("hyposmia") OR ("anosmia") OR ("dysosmia") OR ("parosmia")) AND (ALL("COVID-19") OR ALL("coronavirus") OR ALL("SARS-CoV2") or ALL("COVID")) AND (ALL("olfactory training") OR ALL("olfactory rehabilitation") OR ALL("olfactory education") OR ALL("smell training") OR ALL("smell education") OR ALL("intranasal") OR ALL("INCS") OR ALL("corticosteroids") OR ALL("steroids") OR ALL("mometasone furoate") OR ALL("fluticasone fluroate") OR ALL("triamcinolone acetonide") OR ALL("budesonide") OR ALL("treatment") OR ALL("intervention") OR ALL("therapy") OR ALL("Zinc") OR ALL("Vitamin A") OR ALL("omega 3") OR ALL("Retinoic acid") OR ALL("alpha lipoic acid"))		3850
Ovid	#	**Query**	**Results from 30 Apr 2022**	561
	1	Rhinitis/ or Olfaction Disorders/ or olfactory disorders.mp. or Smell/ or Sinusitis/	46,554	
	2	Olfaction Disorders/ or Smell/ or olfactory dysfunction.mp.	21,351	
	3	Olfaction Disorders/ or olfactory loss.mp. or Smell/	20,721	
	4	smell dysfunction.mp. or Olfaction Disorders/	5,222	
	5	smell disorders.mp. or Olfaction Disorders/	5,234	
	6	smell loss.mp. or Anosmia/	646	
	7	anosmia.mp. or Olfaction Disorders/ or Anosmia/	7,591	
	8	hyposmia.mp. or Anosmia/	2,071	
	9	Olfaction Disorders/ or parosmia.mp.	5,228	
	10	dysosmia.mp. or Olfaction Disorders/	5,273	
	11	covid-19.mp. or COVID-19/	241,887	
	12	SARS-CoV-2/ or COVID-19/ or Coronavirus Infections/ or Sars-CoV2.mp.	166,124	
	13	coronavirus.mp. or Coronavirus/	127,727	
	14	COVID-19/ or covid.mp.	243,115	
	15	11 or 12 or 13 or 14	262,173	
	16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	49,948	
	17	corticosteroids.mp.	76,439	
	18	steroids.mp. or Steroids/	123,085	
	19	Administration, Intranasal/ or intranasal.mp.	30,957	
	20	intranasal corticosteroids.mp. or Administration, Intranasal/	16,318	
	21	mometasone.mp. or Mometasone Furoate/	1,279	
	22	fluticasone.mp. or Beclomethasone/ or Fluticasone/	7,694	
	23	Triamcinolone Acetonide/ or Triamcinolone/ or triamcinolone.mp.	12,519	
	24	prednisolone.mp. or Prednisolone/	48,665	
	25	olfactory training.mp.	174	
	26	smell training.mp.	22	
	27	Zinc Sulfate/ or Zinc/ or zinc.mp.	168,172	
	28	Dietary Supplements/ or omega 3.mp.	89,510	
	29	Dietary Supplements/ or vitamin A.mp. or Antioxidants/ or Ascorbic Acid/	267,828	
	30	therapy.mp. or Therapeutics/	5,699,529	
	31	therapy.mp. or Therapeutics/	5,699,529	
	32	treatment.mp. or Therapeutics/	5,471,318	
	33	intervention.mp.	737,522	
	34	Budesonide/	4,794	
	35	alpha lipoic acid.mp. or Thioctic Acid/	5,439	
	36	retinoid acid.mp.	522	
	37	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	9,230,554	
	38	15 and 16 and 37	577	
	39	limit 38 to dt=20150101-20220331 [January 1st, 2015 to March 31st, 2022]	561	
Cochrane	Olfactory dysfunction, olfactory loss			57
World Health Organization (WHO) COVID-19 'Global literature on coronavirus disease	((("olfactory disorders") OR ("olfactory dysfunction") OR ("olfactory loss") OR ("smell disorders") OR ("smell dysfunction") OR ("smell loss") OR ("hyposmia") OR ("anosmia") OR ("parosmia") OR ("dysosmia"))) AND ((("olfactory training") OR ("smell training") OR ("treatment") OR ("therapy") OR ("intervention") OR ("intranasal") OR ("intranasal corticosteroids") OR ("steroids") OR ("prednisolone") OR ("mometasone fluroate") OR ("fluticasone") OR ("triamcinolone") OR ("Budesonide") OR ("Zinc") OR ("Vitamin A") OR ("Retinoic acid") OR ("Omega 3") OR ("alpha lipoic acid")))			1134
MedRxiv	((("olfactory disorders") OR ("olfactory dysfunction") OR ("olfactory loss") OR ("smell disorders") OR ("smell dysfunction") OR ("smell loss") OR ("hyposmia") OR ("anosmia") OR ("parosmia") OR ("dysosmia"))) AND ((("olfactory training") OR ("smell training") OR ("treatment") OR ("therapy") OR ("intervention") OR ("intranasal") OR ("intranasal corticosteroids") OR ("steroids") OR ("prednisolone") OR ("mometasone fluroate") OR ("fluticasone") OR ("triamcinolone") OR ("Zinc") OR ("Vitamin A") OR ("Omega 3")))			31

JBI critical appraisal checklist for case series.

	Yes	No	Unclear	Not applicable
Q1. Were there clear criteria for inclusion in the case series?	☐	☐	☐	☐
Q2. Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	☐	☐	☐
Q3. Were valid methods used for identification of the condition for all participants included in the case series?	☐	☐	☐	☐
Q4. Did the case series have consecutive inclusion of participants?	☐	☐	☐	☐
Q5. Did the case series have complete inclusion of participants?	☐	☐	☐	☐
Q6. Was there clear reporting of the demographics of the participants in the study?	☐	☐	☐	☐
Q7. Was there clear reporting of clinical information of the participants?	☐	☐	☐	☐
Q8. Were the outcomes or follow up results of cases clearly reported?	☐	☐	☐	☐
Q9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	☐
Q10. Was statistical analysis appropriate?	☐	☐	☐	☐

JBI critical appraisal checklist for analytical cross sectional studies.

	Yes	No	Unclear	Not applicable
Q1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
Q2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
Q3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
Q4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
Q5. Were confounding factors identified?	☐	☐	☐	☐
Q6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
Q7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
Q8. Was appropriate statistical analysis used?	☐	☐	☐	☐