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Pediatric Dermatology and Allergy (J Lee, Section Editor)

Management of post-COVID-19 olfactory dysfunction

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Abstract

Purpose of Review Olfactory dysfunction is a frequent complication of SARS-CoV-2 infection. This review presents the current literature regarding the management of post-COVID-19 olfactory dysfunction (PCOD).

Recent Findings A systematic review of the literature using the PubMed/MEDLINE, EMBASE, and Cochrane databases for the following keywords, "Covid-19," "SARS-CoV-2," "anosmia," "olfactory," "treatment," and "management" was performed. While most cases of post-COVID-19 olfactory dysfunction resolve spontaneously within 2 weeks of symptom onset, patients with symptoms that persist past 2 weeks require medical management. The intervention with the greatest degree of supporting evidence is olfactory training, wherein patients are repeatedly exposed to potent olfactory stimuli. To date, no large-scale randomized clinical trials exist that examine the efficacy of pharmacologic therapies for PCOD. Limited clinical trials and prospective controlled trials suggest intranasal corticosteroids and oral corticosteroids may alleviate symptoms.

Summary Olfactory training should be initiated as soon as possible for patients with PCOD. Patients may benefit from a limited intranasal or oral corticosteroid course. Further research on effective pharmacologic therapies for PCOD is required to manage the growing number of patients with this condition.

Introduction

Post-coronavirus disease 2019 (COVID-19) olfactory dysfunction (PCOD) is thought to occur as a result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) damaging the olfactory neuroepithelium [1, 2]. Several studies have hypothesized that this damage is mediated by viral invasion of ACEII and TMPRSS2 receptors on cells in the nasal and olfactory epithelium [3–5]. MRI studies have shown co-occurrence of transient olfactory bulb edema with PCOD, suggesting that an inflammatory response to this viral invasion may contribute to symptomatology as well [6].

Anosmia often represents the first or only symptom of COVID-19 disease, and it is estimated to be present in 19–68% of patients, often independently of coryzal symptoms [2, 7–9]. Any degree of olfactory dysfunction (OD) is estimated to be present in a larger majority, with up to 85–98% of patients affected in some studies [1, 2]. The natural course of PCOD is spontaneous resolution by two weeks for 95% of patients, with mean recovery of 9 days [9, 10]. However, in some patients, persistent PCOD is a prevalent symptom, appearing in 75% of cases with persistent COVID symptoms [11]. Risk factors for persistent PCOD include older age, diabetes mellitus, and longer duration of COVID-19 illness [9]. In light of the global prevalence of COVID-19, even a small proportion of patients with persistent PCOD likely numbers in the millions. Physicians face the challenge of managing an unprecedented number of patients with PCOD in the coming years.

The impacts of PCOD on quality of life are significant. PCOD reduces a person's ability to enjoy foods and fragrances, recall olfaction-associated memories, and detect hazardous materials such as spoiled food and toxic fumes [12]. Furthermore, it is associated with a range of debilitating psychosocial effects, including depression, social isolation, impaired cognition, decreased nutrition, and earlier death [13•].

There is strong evidence supporting the use of olfactory training (OT) in the management of PCOD, with most studies demonstrating greater improvements in olfactory function (OF) with earlier initiation of therapy [13•, 14••]. However, there has been no consensus on appropriate pharmacotherapy for treatment of PCOD. Some limited randomized control trials have demonstrated benefit with short-term topical or oral corticosteroid use, but to date, there have been no large-scale trials investigating their efficacy [15–18]. Other therapies used in non-COVID-19 OD, such as theophylline, vitamin A, omega-3, or zinc, have been investigated but lack compelling evidence in favor of their use [19••].

The following studies employed a variety of olfactory tests to assess OF in response to treatment. Some studies used the Sniffin' Sticks test, which uses felt-tip pens to present various concentrations of odorants to assess a subject's odor threshold, discrimination, and identification. In this test, OF is measured using the threshold, discrimination, and identification (TDI) score [20]. The University of Pennsylvania Smell Identification Test (UPSIT) is another widely used, well-validated olfactory test, in which a subject is asked to identify 40 scratch-and-sniff odors in a test booklet [21]. Other tests include the objective Connecticut Chemosensory Clinical Research Center (CCCRC) test as described by Cain et al. [22] and the subjective Visual Analog Scale (VAS) as described by McCormack et al. [23]. In all of these tests, higher scores indicated better OF.

Treatment

Diet and Lifestyle

For patients with PCOD, counseling should be provided to maximize quality of life, nutrition, and safety. Patients should be strongly encouraged to ensure proper functioning of smoke and natural gas detectors to facilitate early detection of warning smells [24], class 2A]. They should also be advised to exercise

caution in food safety by monitoring food expiration dates as well as to monitor overall nutritional intake [24], class 2A]. In active smokers, smoking cessation has been suggested to improve olfactory symptoms in patients with post-infectious olfactory disorders (PIOD) [19••], class 2A]. Traditional Chinese acupuncture has also been studied in limited low-level studies (1 level 3 study; 1 level 4 study), showing clinically significant improvements in TDI and UPSIT scores among a small group of patients with minimal treatment-related risk [13•], class 4].

Patients with OD have also demonstrated higher rates of depression than normosmic patients, suggesting a need for early recognition, screening, and intervention including referral to mental health services when appropriate [24], class 2A].

First-Line Therapy

Olfactory Training

The therapy for treatment of PCOD with the greatest evidentiary support is olfactory training (OT). OT is a non-pharmacologic treatment option involving repeated odor exposure, with promising outcomes for treatment of PVOD [Table 1]. The mechanism of action for this therapy is largely hypothetical but is thought to be related to regeneration of olfactory receptor neurons and/or improved higher order processing of olfactory information [25], level 4]. A position paper by Hummel et al. recommended OT in patients with olfactory loss of several etiologies, given the demonstrated benefits seen in several studies [26], level 5].

Classical OT protocols include twice-daily exposure to a set of 4 intense odors, including rose, eucalyptus, lemon, and cloves over a period of 12 weeks [20], level 2B]. In the morning and evening, patients smell each odorant for 10 s, rotating through all 4 odors to finish the set. Since the inception of OT, modified OT protocols have allowed patients to purchase their own essentials oils with varying odor concentrations and combinations, which have been shown to increase patient compliance and adherence while still achieving clinically significant improvements in olfactory function [14••], level 2A; 28, level 2B]. Modified OT protocols have tested a wider variety of odors and longer durations of therapy with improved outcomes [14••], level 2A; 25, level 4]. Conversely, therapy durations of less than 12 weeks may be ineffective [17], level 2B].

Denis et al. described a trial wherein 548 participants underwent olfactory training with concurrent visual depictions of the scents. After 4 weeks, 64% of patients reported improved symptoms [27], level 1B]. Though this study was limited by the lack of a control cohort, the results demonstrated that a large proportion of patients experienced clinically significant benefit from OT. Several meta-analyses published by Hura et al., Kattar et al., and Addison et al. all came to similar conclusions, as evidenced in Table 1 [13•], level 1A; 14••, level 2A; 19••, level 2A]. Hura et al. reviewed 10 studies, including 5 randomized controlled trials (RCTs), which demonstrated that OT resulted in

Table 1 Studies comparing effectiveness of olfactory training

Study/year	Level of evidence	Study design	Results	Conclusions
Studies on PCOD				
Denis et al. 2021 [27]	1B	- 548 patients with at least 1 month of PCOD were exposed to OT twice daily assisted by a web application displaying pictures correlated with the odorants for at least 7 days	- 64% of patients showed a clinically significant improvement after a mean olfactory training of 28 days - Patients who trained for longer than 28 days experienced better outcomes - Hyposmic patients exhibited improved outcomes after OT compared to anosmic patients	- OT was effective in most patients with PCOD in clinically improving OF - Training for longer than 28 days may lead to improved outcomes - Hyposmic patients had improved prognosis than anosmic patients
Studies on PVOD/PIOD				
Hura et al. 2020 [13•]	1a	- Systematic review of OT outcomes among patients with PVOD - 10 studies analyzed, including 2 large RCTs (level 1b), 2 small RCTs (level 2b), 3 prospective cohort studies (level 3), and 3 prospective/retrospective case series (level 4 studies)	- OT resulted in improved TDI and UPSIT scores - Minimal adverse effects (inconvenience of daily training) were seen	- OT for a minimum of 12 weeks is a recommendation for treatment of PVOD. OT is an inexpensive option with minimal/no harm and high benefit

Table 1 (continued)

Study/year	Level of evidence	Study design	Results	Conclusions
Kattar et al. 2021 [14••]	2a	- Systematic review of OT outcomes among patients with PVOD - 4 studies analyzed, including 2 RCTs (level 1b) and 2 prospective non-randomized controlled studies (level 2b)	- Nearly threefold greater odds of achieving a clinically significant improvement in TDI scores among patients undergoing OT compared to controls (OR 2.77; 95% CI 1.67–4.58), even after accounting for variability in OT protocols among the 4 studies - Longer durations of OT (up to 56 weeks), along with shorter durations of symptoms prior to initiation of OT (<12 months), were associated with greater improvements in olfactory function	- OT for a minimum of 12 weeks improved olfactory function, among patients with PVOD - The strengths of OT included ease of implementation and minimal adverse effects - The limitations of OT included a lack of consensus regarding the optimal duration of therapy, dependence on high patient compliance (sustained daily training for months), and long-term effectiveness of therapy (>56 weeks)
Addison et al. 2021 [19••]	2A	- Meta-analysis of 40 studies, including 11 RCTs investigating PIOD	- 3 meta-analyses of RCTs, cohort studies, and prospective controlled studies showed long-term (>32 weeks) and high-concentration deodorants improved olfactory function among patients who had OT	- OT had significant evidence of benefit for patients with generalized anosmia

Table 1 (continued)

Study/year	Level of evidence	Study design	Results	Conclusions
Hummel et al. 2017 [26]	5	-Position paper	-Review of 6 studies demonstrated that OT led to improve OF after 12–36 weeks of treatment, with longer durations of treatment and higher odor concentrations resulting in greater improvements in OF -OT was postulated to increase regenerative capacity of olfactory neurons as a result of repeated odorant exposure	-Given low cost and high safety of OT, it was recommended in patients with OD of several etiologies

CI confidence interval
OD olfactory dysfunction
OF olfactory function
OR odds ratio
OT olfactory training
PCOD post-COVID-19 olfactory dysfunction
PIOD post-infectious olfactory dysfunction
PVOD post-viral olfactory dysfunction
RCT randomized controlled trial
TDI score threshold, discrimination, and identification score
UPSIT University of Pennsylvania Smell Identification Test

improved TDI and UPSIT scores, concluding that a minimum of 12 weeks of therapy was recommended for treatment of PVOD [13•], level 1A]. Addison et al. reviewed 40 studies – of which 11 were RCTs – and published similar findings, demonstrating that long-term OT (>32 weeks) with high-concentration odorants conferred significant benefit for patients with generalized anosmia [19••], level 2A]. Kattar et al. reviewed 4 studies including 2 RCTs, concluding that there was a threefold greater chance of achieving a clinically significant improvement in TDI scores among patients undergoing OT compared to controls. This finding also held true after accounting for variability in OT protocols. Additionally, this systematic review found that longer duration of OT (up to 56 weeks) along with earlier initiation of OT following symptoms (<12 months) was associated with greater improvements in olfactory function [14••], level 2A]. Kattar et al., however, acknowledged the current limitations to OT, including a lack of consensus regarding optimal duration of therapy, dependence on high patient compliance, and need for long durations of treatment to achieve therapeutic effect.

Nevertheless, given its limited harm profile, relatively low cost, and evidence of effectiveness, patients should begin OT as soon as possible following symptoms of PCOD and continue therapy for a minimum of 12 weeks [19••, 29], level 2A].

Pharmacologic Treatment

While most cases of PCOD resolve spontaneously within 2 weeks, cases that persist beyond this timepoint may require pharmacologic intervention. Recent MRI studies have demonstrated inflammatory changes in the olfactory clefts of COVID-19 patients with anosmia compared to healthy controls, suggesting a possible role for anti-inflammatory agents such as intranasal corticosteroid sprays and oral corticosteroids [25], level 4]. A position paper by Hummel et al. recommended use of systemic and/or topical steroids in patients with olfactory dysfunction secondary to chronic rhinosinusitis and other inflammatory conditions, also suggesting a role for steroid treatments for PCOD [26], level 5].

Intranasal Corticosteroid Sprays

There is conflicting evidence regarding the efficacy of intranasal corticosteroid sprays (ICS), with some RCTs showing no benefit [18], level 2B], and others demonstrating improvement in olfaction scores following short-term courses of ICS therapy [16, 30], level 2B] [Table 2].

In one of the few RCTs published studying PCOD patients, Abdelalim et al. [18], level 1B] performed a study of 50 individuals who underwent daily mometasone furoate nasal sprays in combination with OT for 3 weeks, compared to 50 patients who underwent OT alone. Patients who underwent added MFNS therapy experienced no significant benefit over OT alone, as

Table 2 Studies comparing effectiveness of intranasal corticosteroid sprays

Study/year	Level of evidence	Study design	Results	Conclusions
Studies on PCOD				
Abdelalim et al. 2021 [18]	1b	- RCT of 50 patients with PCOD who underwent daily MFNS with OT, compared to 50 patients who underwent OT alone, for 3 weeks - Olfactory function was assessed using the VAS. Duration of anosmia was recorded from onset until full recovery. Recovery rates were recorded - Follow-up time was 3 weeks	- VAS smell scores significantly improved in both groups by the 3rd week of treatment ($P<0.001$). There were no significant differences between the groups after 1, 2, or 3 weeks of treatment - The average time until complete recovery in the MFNS + OT group was 26.4 days, compared to 26.2 days in the OT alone group ($P=0.88$) - 62% of patients who underwent MFNS + OT completely recovered their sense of smell after 3 weeks, compared to 52% of patients who underwent OT alone ($P=0.31$)	- Adding MFNS in the treatment of PCOD offers no superiority benefit over OT, regarding VAS smell scores, duration of anosmia, and recovery rates
Hopkins et al. 2021 [15]	5	- Expert consensus statement based on literature review conducted via Medline and Cochrane databases	- Consensus of 15 experts agreeing that topical intranasal corticosteroids might aid in PCOD	- ICS is recommended in patients with anosmia lasting longer than 2 weeks
Singh et al. 2021[30]	3B	- Prospective interventional study of 120 patients with PCOD - OF tested at days 1 and 5 after positive RT-PCR - 60 patients given 2 sprays fluticasone every day for 5 days	- Symptoms of anosmia and dysgeusia improved for patients receiving ICS over those in the control group ($p<0.001$)	- In the acute setting, ICS may hasten recovery; however, it is unclear whether these patients would have recovered OF eventually or whether early intervention prevented long-term anosmia given lack of long-term follow-up
Studies on PVOD/PIOD				

Table 2 (continued)

Study/year	Level of evidence	Study design	Results	Conclusions
Hura et al. 2020 [13•]	3a	- Systematic review of PVOD undergoing treatment with ICS - Studies analyzed included 1 RCT (level 1b), 1 case series (level 4), and 1 retrospective review (level 4)	- Some patients (25–58%) with PVOD demonstrated mildly improved olfactory scores after use of ICS - Minimal side effects (local irritation, epistaxis) were seen with ICS use - The RCT included 23 patients who were initially treated with a 10-day course of OCS+ICS, after which they were randomized to continue ICS versus placebo versus control. All patients experienced improvement in olfactory scores after the initial 10-day treatment period. Given co-treatment, this improvement may not be attributed to ICS alone. Patients taking ICS compared to placebo or control showed no difference in olfactory outcomes at 6-month follow-up -The level 4 studies lacked control groups; therefore, it was difficult to determine whether recovery of olfaction was due to spontaneous recovery or the effect of treatment	- Short-term ICS use is an option for management of PVOD due to the mild benefit seen in some patients and overall low risk of therapy. If there is no initial improvement after ICS use, then there is limited evidence suggesting benefit with chronic use

Table 2 (continued)

Study/year	Level of evidence	Study design	Results	Conclusions
Addison et al. 2021 [19••]	2A	- Meta-analysis of 40 studies, including 11 RCTs investigating PIOD	- 1 prospective case series showing benefit of ICS in 2 of 8 patients - 1 prospective study showing intranasal injection leading to 50% improvement - 1 observational study using topical steroids with 58% self-reporting improvement in symptoms - Studies examined were mostly conducted on PVOD patients before COVID-19 pandemic and may not be specific to PCOD	- ICS may alleviate symptoms in patients without spontaneous improvement in olfaction - Kaiteki position in which patients lie on the side with their head tilted may have more efficacy by allowing nasal drops to reach the olfactory cleft

ICS intranasal corticosteroid spray
MFNS mometasone furoate nasal sprays
OCS oral corticosteroid
OF olfactory function
OT olfactory training
PCOD post-COVID-19 olfactory dysfunction
PICD post-infectious olfactory dysfunction
PVOD post-viral olfactory dysfunction
RCT randomized controlled trial
VAS visual analog scale

measured by smell scores, duration of anosmia, and recovery rates. However, the time since onset of OD symptoms was not standardized among the patients of this study. Given that patients experience variable recovery depending on the time of therapy initiation after infection, this study does not exclude the possibility of a subset of patients that, when treated early in their clinical course, might benefit from ICS.

Several consensus statements have recommended ICS for patients with PCOD symptoms lasting longer than 2 weeks [15, level 5; 19••, level 2A]. Hopkins et al. reported the consensus statement of the British Rhinological Society, integrating information from a literature review of post infectious olfactory dysfunction graded by 15 experts [15], level 5]. Multiple studies reviewed by Hopkins et al. demonstrated no additive benefit to topical steroids when used in combination with oral steroids. However, another retrospective study cited by Hopkins et al. noted combination of ICS with olfactory training was more therapeutic than olfactory training alone. Ultimately, Hopkins et al. recommended ICS for PCOD symptoms persisting past 2 weeks [19••], level 2A].

Interestingly, one study reported by Hopkins et al. demonstrated a benefit with budesonide irrigations, leading the authors to suggest that sufficient contact of areas of inflammation was necessary to achieve therapeutic effect [19••], level 2A]. In a similar vein, some authors have suggested that nasal irrigation, rather than sprays, may be more effective at treating PCOD due to increased penetration to the olfactory cleft [31], level 2B]. To this end, some have suggested the use of the Kaiteki position, wherein patients lay on their side with the head tilted and chin lifted at a 20 to 40 degree angle, such that nasal drops may reach the olfactory cleft [32], level 4].

Addison et al. reported on the consensus statement of the Clinical Olfactory Working Group based on 15 articles evaluating management of post-infectious olfactory dysfunction [19••], level 2A]. This group concluded that, though direct evidence of the utility of ICS was limited, the relative risk of ICS was low enough such that a trial of ICS was advisable for most patients. Like the studies analyzed by Hopkins et al., many of the papers analyzed by Addison et al. tested the efficacy of ICS in combination with other therapies. As such, there has been limited evidence of the use of ICS alone. Importantly, Addison et al. concurred with Hopkins et al. in concluding that effective delivery of topical corticosteroids could play a limiting factor in the efficacy of ICS and suggested that patients might benefit from usage of the Kaiteki position [19••], level 2A].

A systematic review by Hura et al. included three studies that looked into the utility of topical corticosteroid sprays, of which one was a RCT performed by Blomqvist et al. in 2003 among patients with post-viral olfactory dysfunction [13•], level 1A]. In this RCT, 23 patients were treated with a 10-day course of ICS and oral corticosteroids (OCS), after which they were randomized to continued ICS, placebo, or control groups. The study demonstrated no differences in outcome in olfactory function at 6 months among the three groups, suggesting limited benefit in chronic use of ICS. However, in two other case series analyzed by Hura et al., topical application of corticosteroids was investigated and found to cause some improvement in olfactory dysfunction. Though this effect was only seen in a subset of patients (25–58%), Hura

et al. concluded that the limited side effects of topical corticosteroids and the possibility of therapeutic effect made ICS preferable to oral corticosteroids for many patients [13•], level 1A].

In summary, though the evidence to support use of ICS in PCOD patients is mixed both in strength and applicability to post-SARS-CoV2 patients, the side effect profile of this therapy is limited; as such, for most patients, the potential benefits likely outweigh the risks for a short-term trial. Drug information for intranasal corticosteroids is provided in Table 3.

Oral Corticosteroids

There is limited evidence to support the use of oral corticosteroids (OCS) in PCOD [Table 4]. Consensus statements published by Hopkins et al. and Addison et al. advised that, though OCS have evidence of effectiveness, they have a limited role in routine clinical management of PCOD due to their extended side effect profile [15], level 5; 19••, level 2A]. One retrospective study analyzed by Addison et al. was performed on patients with any cause of olfactory dysfunction and showed the combination of OCS + ICS or OCS alone was more effective at treating PCOD than ICS alone [19••], level 2A]. The consensus statement released by Addison et al. also discussed an RCT in which patients with post-infectious olfactory dysfunction were initially treated with oral prednisolone before transitioning to ICS. This investigation found that the initial course of oral steroids was effective at reducing PCOD symptoms, while the subsequent course of topical steroids conferred no additional advantage [19••], level 2A]. Another study included by Addison et al. showed an oral methylprednisolone taper was able to improve olfactory dysfunction of all etiologies [19••], level 2A]. However, these studies were all limited by lack of specificity to PCOD. Moreover, several studies reported by Addison et al. were performed on patient populations with olfactory dysfunction of non-infectious origins and thus cannot be readily generalizable to the PCOD patient set. Both consensus statements published by Addison et al. and Hopkins et al. agreed that, due to the multi-system nature of

Table 3 Drug information for intranasal corticosteroids

Mometasone furoate or fluticasone propionate	
Standard dosage	2 sprays (100ug) of mometasone or fluticasone daily in each nostril for 3 weeks
Contraindications	Current or past tuberculosis, infections of any type (virus, bacteria, fungus, amoeba), glaucoma, cataracts, nasal ulcers
Main drug interactions	None
Main side effects	Nasal/throat irritation, dryness, epistaxis
Special points	Differences in the type, dosing, and duration of intranasal corticosteroid sprays vary among studies
Cost/cost-effectiveness	$30–$60 per month

Table 4 Studies comparing effectiveness of systemic corticosteroids

Study/year	Level of evidence	Study design	Results	Conclusions
Studies on PCOD				
Le Bon et al. 2021 [17]	2b	- Non-randomized prospective controlled trial of 9 COVID-19 patients undergoing a 10-day course of OCS+OT, compared to 18 COVID-19 patients undergoing OT alone - Therapy was initiated 5 weeks after onset of olfactory dysfunction. Follow-up time was 10 weeks after treatment	- Greater improvement in TDI score among patients undergoing OCS+OT, compared to OT alone ($P=0.046$) - The authors reported a low level of compliance for OT (<50%) - 3 patients reported mild side effects to OCS including abdominal pain and insomnia	- This pilot study suggests a combination of OCS+OT is safe and beneficial for treatment of PCOD, compared to OT alone
Vaira et al. 2020 [16]	2B	- Non-randomized RCT with 18 patients with PCOD for more than 30 days - 9 patients treated with systemic prednisone and nasal irrigation with betamethasone for 15 days - 9 patients were otherwise untreated	- Patients showed no improvement at 20 days - Treatment group had greater improvement in olfactory scores at 40 day evaluations - Study limited by small sample size and unevenly distributed treatment groups	- Refractory anosmia may respond to combination of ICS and OCS - Treatment difference may manifest weeks after initial therapy
Huart et al. 2021 [29]	2A	- Delphi process performed on experts from the Clinical Olfaction Working Group	- General efficacy of OCS remains controversial; evidence to support OCS is level 4 - OCS may potentially inhibit neuronal regeneration of olfactory epithelium	- Selected patients may benefit from systemic corticosteroids given signs of nasal inflammation - There is a lack of evidence of clear benefit for patients taking OCS, and they should be used with caution according to patient circumstances
Studies on PVOD/PIOD				

Table 4 (continued)

Study/year	Level of evidence	Study design	Results	Conclusions
Hura et al. 2020 [13•]	3a	- Systematic review of OCS in management of PVOD - 6 studies analyzed, including 1 prospective case–control study (level 3b) and 5 retrospective reviews (level 4)	- Short-term (~2 weeks with taper) OCS resulted in mildly improved olfactory scores across multiple psychophysical tests, at a cost of potential side effects related to OCS -Studies lacked control groups; therefore, it was difficult to determine whether recovery of olfaction was due to spontaneous recovery or the effect of treatment - A retrospective review by Kim et al. with 491 patients demonstrated that patients taking MFNS alone were less likely to recover olfactory function (28.2% recovery rate), compared to those taking oral prednisolone with MFNS (54.8% recovery rate) or those taking oral prednisolone alone (55.0% recovery rate) after 1-month follow-up ($P<0.001$) - A retrospective review by Schriever et al. showed a significant increase in TDI score ($P=0.003$) after 2 weeks of oral methylprednisolone treatment, although there was no control group and the increase in TDI score failed to reach the minimal clinically importance difference	- Short-term OCS (~2 weeks with taper) are an option in select patients with PVOD, after consideration of the potential risks of oral steroids in the setting of medical comorbidities

Table 4 (continued)

Study/year	Level of evidence	Study design	Results	Conclusions
Addison et al. 2021 [19••]	2A	- Meta-analysis of 40 studies, including 11 RCTs investigating PIOD	- Retrospective study showing improvement of OD with OCS and combination OCS with ICS, over ICS alone in general OD - RCT showing 40 mg prednisolone can lead to improve OF in PVOD - Oral methylprednisolone 40 mg showed improvement in general OD - Observational study showing no improvement in patients given oral prednisolone after failing ICS in general OD	- Oral corticosteroids may show some efficacy in PCOD patients as they have shown some success in improving anosmia in post-infectious OD - Patients who have failed ICS may not respond to OCS

MFNS mometasone furoate nasal sprays
OCS oral corticosteroids
OD olfactory dysfunction
OT olfactory training
PCOD post-COVID-19 olfactory dysfunction
PIOD post-infectious olfactory dysfunction
PVOD post-viral olfactory dysfunction
TDI score threshold, discrimination, and identification score

SARS-CoV2, multidimensional risk benefit analysis should occur before initiation of oral steroid therapy. However, Hopkins et al. stated that a short trial of oral corticosteroids could be appropriate in the scenario where olfactory dysfunction is the only symptom of SARS-CoV2 [19••], level 2A].

Several studies exist examining the effect of oral steroids more specifically in PCOD patients. A non-randomized controlled trial by Le Bon et al. [17], level 2B] showed greater improvements in olfactory scores among PCOD patients undergoing OCS and olfactory training (OT), compared to OT alone. However, this trial studied 27 patients, of which only 9 were treated with oral corticosteroids, thereby limiting its statistical power. Vaira et al. reported on a non-randomized control trial testing the efficacy of the combination of systemic prednisone and ICS in patients with PCOD persisting longer than 30 days. This study found significant improvement at 40 days of treatment, suggesting that long-term courses of OCS and intranasal steroid irrigation could prove useful for refractory cases [8], level 2B].

Hura et al. aggregated six studies of OCS to show that patients experienced quantifiable improvement in olfaction, but concluded that consideration of OCS was patient- and situation-dependent, given the broad side effect profile [13•], level 3A]. Similarly, Addison et al. stated that while OCS had some evidence of clinical utility, clinicians were divided on its routine use in a PCOD setting; the authors suggested the alternative of a short 3–4-day course of OCS to trial therapy responsiveness before beginning a more prolonged course [19••], level 2A].

Ultimately, though the side effect profile limits its applicability, evidence suggests OCS may be an effective option in some patients with persistent PCOD symptoms. Furthermore, several trials in the literature suggest the

Table 5 Drug information for oral corticosteroids

Oral prednisolone	
Standard dosage	Option 1) 30 mg/day × 3 days, followed by 20 mg/day × 4 days, followed by 10 mg/day × 7 days OR Option 2) 40 mg/day × 14 days, followed by a taper (daily reduction of 5 mg)
Contraindications	Diabetes, hypertension, kidney disease, cardiovascular disease, liver disease, under- or over-active thyroid, neuropsychiatric disease, osteoporosis or any other bone disease, stomach or intestine problems, current or past tuberculosis, infections of any type (virus, bacteria, fungus, amoeba), myasthenia gravis, glaucoma, cataracts, mental disorders, pregnancy
Main drug interactions	Mifepristone, drugs that can cause bleeding/bruising (aspirin, coumadin), other systemic corticosteroids, immunosuppressants, immune modulators, certain antibiotics, antiseizure medications, anticholinesterase medications
Main side effects	Nausea/vomiting, heartburn, headache, dizziness, menstrual period changes, insomnia, fatigue, weight gain, fluid retention, hypertension, cataracts, glaucoma, easy bruising/bleeding, acne, reduced immune response and ability to fight infections, adrenal suppression, hyperglycemia, mental/mood changes, muscle weakness/pain, skin thinning, slow wound healing, bone pain or fractures, stomach/intestinal bleeding, trouble breathing, seizures
Special points	Differences in the type, dosing, and duration of oral corticosteroids vary among studies
Cost/cost-effectiveness	Inexpensive ($10–20 per course)

combination of OCS and ICS may prove useful for refractory cases of olfactory dysfunction. Drug information for oral corticosteroids is provided in Table 5.

Declarations

Conflict of Interest
The authors declare no competing interests.

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•• Of major importance

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