

Pharmacologic treatment for postviral olfactory dysfunction: a systematic review

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Background: Postviral olfactory dysfunction (PVOD) is the most common cause of olfactory dysfunction. Several treatments have been presented in the literature. The objective of this study is to systematically review the existing literature on the effectiveness of pharmacologic treatments for PVOD.

Methods: We performed a literature search of PubMed, Ovid, and ScienceDirect from 1966 to 2014. Inclusion criteria included English-language articles containing original data on pharmacologic treatment of PVOD with ≥ 5 subjects, measurable outcomes, and readily available treatments. Data was collected regarding study design, subject demographic information, clinical outcomes, and level of evidence. Two investigators reviewed all articles independently.

Results: Of 445 abstracts identified, 8 articles were included, yielding 563 patients. Treatments investigated included oral corticosteroids, local injections of corticosteroids, zinc sulfate, alpha lipoic acid, caroverine, vitamin A, *Ginkgo biloba*, and minocycline. Outcome measures were determined by symptom scores and objective olfactory test methods—the most common being Sniffin' Sticks.

Improvement was noted in subjects receiving oral corticosteroid therapy, local injections of corticosteroid, alpha lipoic acid, and caroverine, whereas vitamin A, zinc sulfate, *Ginkgo biloba*, and minocycline groups did not show significant improvement.

Conclusion: The majority of therapies investigated that show benefit in treating PVOD are of poor quality. Although caroverine therapy showed benefit and is a level 1b study, etiologies of olfactory dysfunction other than PVOD were included as well, which clouds the results. Overall, there is no strong evidence for any pharmacologic treatment of PVOD in the literature. © 2016 ARS-AAOA, LLC.

Key Words:

postviral olfactory dysfunction; postinfectious; olfactory dysfunction; anosmia; hyposmia; pharmacotherapy; drug treatment

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Olfactory dysfunction can be a troublesome condition—it is often difficult to discern the etiology and even more challenging to manage. A decreased sense of smell significantly dulls interpretation of the world in a myriad of ways. Spoiled food is less likely to be detected. Taste can be dampened resulting in decreased food enjoyment, missed meals, and nutritional deficits. Signs of potentially dangerous situations, such as a gas leak or burning stove,

may be missed. Hyposmia and anosmia have also been shown to have a negative impact on quality of life and mood, resulting in higher rates of depression.¹

There are numerous etiologies of acquired olfactory dysfunction. The most common causes include postviral, post-traumatic, and sinonasal disease.² It is difficult to accurately gauge the prevalence of olfactory dysfunction due to the inherent bias in most studies, which are conducted at clinics that treat mainly olfactory disorders. One epidemiologic study reported the prevalence of self-reported olfactory dysfunction as 0.94% to 4.71%, which increased with age.³ The focus of this article is on olfactory dysfunction due to a viral upper respiratory tract infection. Postviral olfactory dysfunction (PVOD) is the most common cause of olfactory dysfunction.² The incidence of PVOD varies with season.⁴ The severity of smell dysfunction can be mild to complete and the effects can be permanent.

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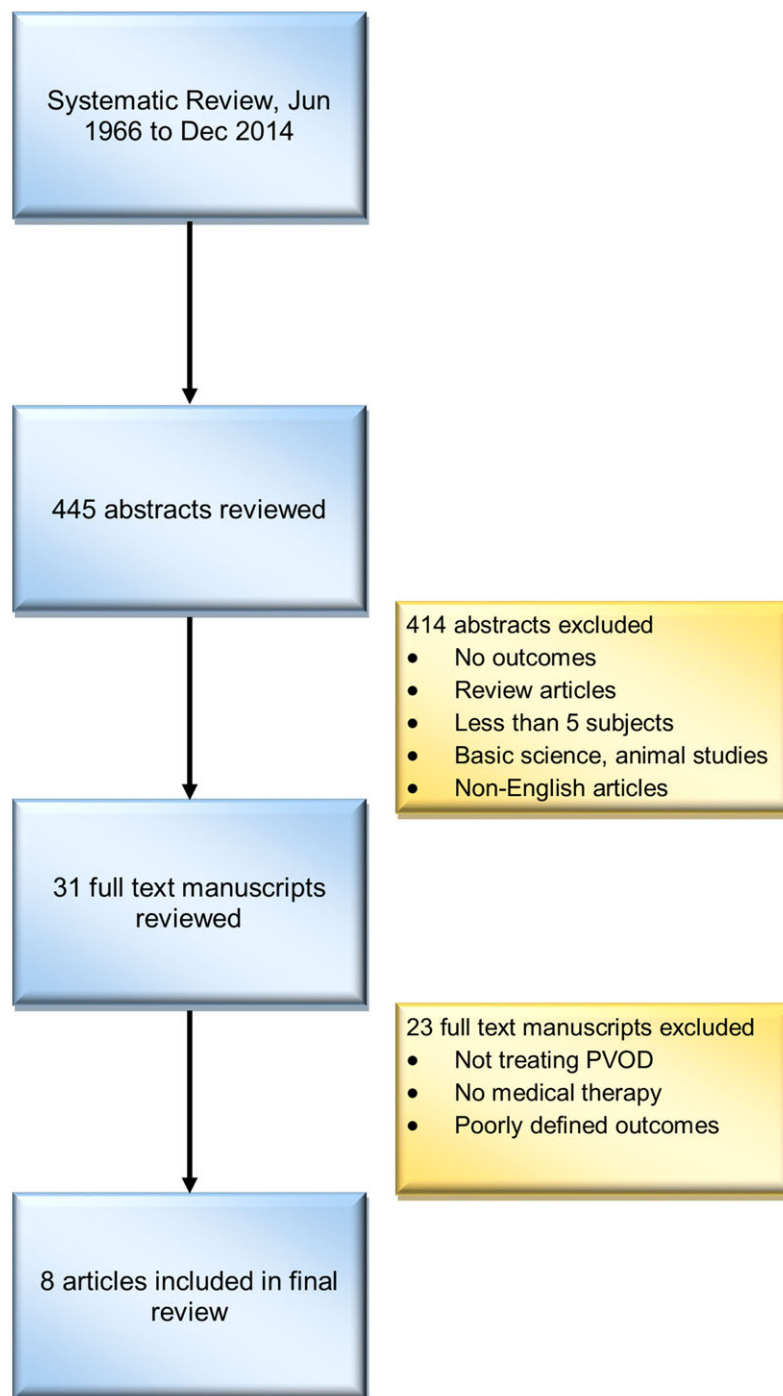


FIGURE 1. Literature search algorithm. PVOD = postviral olfactory dysfunction.

The armamentarium of medical treatment for PVOD is limited. The most common treatment is corticosteroids, both systemic and topical. Some other pharmacologic treatments, such as alpha lipoic acid and local injection of corticosteroids around the olfactory cleft have been reported in the literature, but have not gained widespread acceptance. This is likely due to the majority of studies being small or of low quality. The objective of this article is to perform a systematic review of the literature for medi-

cal treatments of PVOD to help determine the efficacy of different pharmacologic treatments for this condition.

Methods

The study selection process is illustrated in Figure 1. We performed a qualitative review of the published literature using PubMed, Ovid, and ScienceDirect databases to search for pharmacologic methods of treating PVOD. A

quantitative meta-analysis was not performed due to the small size and heterogeneity of the majority of the studies. In December 2014, we searched these databases for articles published from June 1966 to December 2014. General search terms were defined and used in PubMed then applied to the other databases. Search terms used included: olfaction dysfunction, anosmia, hyposmia, pharmacotherapy, therapeutics, drug treatment, postviral, and infectious. Further articles were discovered by examining source lists of the reviewed articles.

Inclusion criteria included English language articles containing original data on pharmacologic treatment of PVOD with ≥ 5 subjects, measurable outcomes, and readily available treatments. Review articles and studies focusing on other causes of olfactory dysfunction were excluded. Articles focusing on nonpharmacologic medical treatments were also excluded. Data was collected regarding study design, subject demographic information, clinical outcomes, and level of evidence. A summary of the included studies can be found in Table 1. Two investigators reviewed all articles independently. Quality assessment was performed on included articles using the Modified Cochrane Collaboration Tool for Assessing Risk of Bias for level 1 and level 2 evidence studies (Table 2) and the Newcastle-Ottawa Assessment Scale for level 3 and level 4 evidence studies (Table 3).

Results

Our literature search yielded 445 abstracts and ultimately 8 articles that met inclusion criteria. A summary of the included articles is displayed in Table 1.

There were 563 patients included across the studies. Subjects were primarily adults with an average age of 54.7 years with a female to male ratio of 2.6 to 1. Severity of symptoms was highly variable from mild hyposmia to anosmia. Time from onset to treatment of PVOD varied from less than 1 month to 183 months. Outcome measures were determined by symptom scores and objective olfactory test methods—the most common being Sniffin' Sticks. The most common scoring system used was the threshold, discrimination, identification (TDI) system.

Length of follow-up ranged from 1 month to 11 months, with an average of 3.25 months. Two articles did not mention follow-up time.^{5,6} Three articles were of level 1b evidence^{7–9} (eg, randomized controlled studies), 2 articles were of level 3b evidence^{10,11} (eg, case-control studies), the remaining 3 articles were of level 4 evidence^{5,6,12} (eg, case series without controls).

Medical therapies investigated included oral methylprednisolone,⁶ vitamin A,⁹ minocycline,⁸ *Ginkgo biloba*,¹¹ dexamethasone or betamethasone injection into the olfactory cleft,⁵ caroverine,⁷ alpha lipoic acid,¹² and zinc sulfate.¹⁰ Five of the studies had control groups,^{7–11} whereas 3 had no controls.^{5,6,12} All articles included statistical analyses.

Significant improvement was noted in subjects receiving oral corticosteroid therapy (level 4),⁶ local injections of corticosteroid around the olfactory cleft (level 4),⁵ alpha lipoic acid (level 4),¹² and caroverine (level 1b),⁷ whereas the vitamin A (level 1b),⁹ zinc sulfate (level 3b),¹⁰ *Ginkgo biloba* (level 3b),¹¹ and minocycline (level 1b)⁸ groups did not show significant improvement (Table 4).

Corticosteroids

A retrospective, noncontrolled study by Schriever et al.⁶ from 2012 investigated oral methylprednisolone treatment of olfactory disorders. PVOD was listed as the etiology for 27 patients. Treatment was an oral methylprednisolone taper starting at 40 mg daily and tapered down over 14 days. Of those with PVOD, 29.6% showed significant improvement in objective measurements of olfaction. Olfaction was measured using TDI scores with an increase of more than 6 points noted as significant. Improvement remained stable through follow-up, but specific follow-up time is not clear. The group was too small to stratify by response in relation to age, gender, or time length of symptoms. Adverse effects of treatment were not discussed.

A prospective, noncontrolled trial by Fukazawa⁵ investigated injecting corticosteroids intranasally around the olfactory cleft. There were 133 patients with PVOD in the study. The treatment regimen involved injection of dexamethasone or betamethasone at 5 mg per dose and was performed every 2 weeks for 8 to 10 weeks or until improvement was noted. Olfaction was measured using a Toyota and Takagi (T&T) olfactometer and subjectively tracked using a visual analog scale. Average recognition threshold using the T&T olfactometer decreased by at least 1 point in 49.6% of the subjects, thus showing improvement. Subjective visual analog scores also improved from an average of 10.2 to 39.5. Follow-up time is not reported. Adverse effects of treatment were not discussed, but it was stated that no major complication occurred.

Corticosteroids with *ginkgo biloba*

A randomized, noncontrolled, parallel group study by Seo et al.¹¹ from 2009 investigated oral *Ginkgo biloba* supplementation used in conjunction with oral prednisolone and mometasone nasal spray for treatment of PVOD in 71 patients. Treatment regimen included prednisolone at 30 mg daily tapered over 14 days with or without 80 mg of *Ginkgo biloba* 3 times daily for 4 weeks. All patients received mometasone nasal spray, 2 puffs per day. Olfaction was measured using the butanol threshold test (BTT) and the Cross-Cultural Smell Identification Test (CCSIT). The group receiving prednisolone and mometasone alone showed significant improvement in average BTT scores (increase of at least 3 points) in 32% of subjects and 14% showed significant improvement on the CCSIT (increase of at least 3 points). Although the group receiving prednisolone, mometasone, and *Ginkgo biloba* showed

TABLE 1. Summary of studies included in the systematic review

Study (year)	Study type	Level of evidence	Therapy	Patients with PVOD (n)	Follow-up	Olfactory measurement	Results
Schriever et al. ⁶ (2012)	Retrospective case series	4	Methylprednisolone	27	Not listed	Sniffin' Sticks	29.6% improved in TDI by at least 6
Reden et al. ⁹ (2012)	Randomized controlled trial	1B	Vitamin A	32	5 M	Sniffin' Sticks	No difference between placebo and vitamin A
Reden et al. ⁸ (2011)	Randomized controlled trial	1B	Minocycline	55	7 M	Sniffin' Sticks	No difference between placebo and minocycline
Seo et al. ¹¹ (2009)	Randomized, nonblinded, parallel group	3B	Prednisolone with mometasone vs prednisolone with mometasone and <i>Ginkgo biloba</i>	71	1 M	BTT, CCSIT	No difference between group receiving <i>Ginkgo biloba</i> and group not receiving <i>Ginkgo biloba</i>
Fukazawa ⁵ (2005)	Prospective, noncontrolled trial	4	Dexamethasone or betamethasone injection	133	Not listed	Toyota & Takagi olfactometer	49.6% had decrease of 1 point or more on Toyota & Takagi olfactometer
Quint et al. ⁷ (2002)	Randomized controlled proof-of-concept study	1B	Caroverine vs zinc sulfate	38	1 M	Sniffin' Sticks	13/35 anosmics in treatment group improved to have measurable thresholds (6 responders had PVOD), no improved threshold in hyposmics. Identification improved for anosmics and hyposmics but no reference to how many had PVOD.
Hummel et al. ¹² (2002)	Prospective clinical trial, unblinded, no control	4	Alpha lipoic acid	23	3–11 M (mean 4.5 M)	Sniffin' Sticks	35% had increase of TDI by at least 5.5
Aiba et al. ¹⁰ (1998)	Retrospective, nonblinded, noncontrolled, parallel group clinical trial	3B	Zinc sulfate vs zinc sulfate with topical corticosteroid and vitamin B vs topical corticosteroid with vitamin B	184	At least 1 M	Subjective symptoms	No difference between groups

BTT = butanol threshold test; CCSIT = cross-cultural smell identification test; M = month; PVOD = postviral olfactory dysfunction; TDI = threshold, discrimination, identification.

TABLE 2. Quality assessment of level 1 and 2 evidence studies (Modified Cochrane Collaboration Tool for assessing risk of bias)*

Potential source of bias	Scoring per item	Study (year)		
		Reden et al. ⁹ (2012)	Reden et al. ⁸ (2011)	Quint et al. ⁷ (2002)
Was there random allocation of subjects?	Random = 0; nonrandom = 1	0	1	1
Was the allocation scheme concealed?	Concealed = 0; not concealed = 1	0	1	1
Were the interventions concealed from study personnel and participants?	Complete blinding = 0; incomplete blinding = 1	0	0	1
Was incomplete data adequately addresses?	Addressed = 0; not addressed = 1	0	0	0
Did the sponsoring company participate in study design or interpretation?	No involvement = 0; involvement = 1	0	0	0
Were there any other important sources of bias?	None = 0; yes = 1	0	0	0
Total score		0	2	3

*Interpretation of score (minimum possible score is 0, maximum possible score is 6); 0–1 point indicates low risk of bias (least bias, best quality study with valid results); 2–3 points indicate medium risk of bias (susceptible to some bias, but not enough to invalidate results); 4–6 points indicate high risk of bias (most ikbias, worst quality study with significant flaws).

TABLE 3. Quality assessment of level 3 and 4 evidence studies (Newcastle-Ottawa Assessment Scale)[†]

Study (year)	Selection grade (maximum 4 asterisks)	Comparability grade (maximum 2 asterisks)	Exposure grade (maximum 4 asterisks)	Total
Schriever et al. ⁶ (2012)	*	N/A	**	***
Seo et al. ¹¹ (2009)	**	*	***	*****
Fukazawa ⁵ (2005)	*	N/A	*	**
Hummel et al. ¹² (2002)	*	N/A	**	***
Aiba et al. ¹⁰ (1998)	**	*	**	*****

[†]Maximum possible total score (highest quality study) for case control study is 10 asterisks, and maximum possible total score (highest quality study) for case series is 4 asterisks. For assessment of case series articles, questions regarding control group are not applicable. N/A = not applicable.

improvement in 37% of subjects on BTT and 33% of subjects on CCSIT, there was no statistical difference in response rates between treatment groups over the 1-month follow-up time. Adverse effects of treatment were not discussed.

Vitamin A

A randomized controlled study by Reden et al.⁹ from 2012 investigated oral vitamin A supplementation for treatment of olfactory dysfunction due to PVOD or trauma. PVOD was listed as the etiology for 32 patients. Subjects received 10,000 units of vitamin A daily vs placebo. In the vitamin A group 29% showed significant improvement in objective measures of smell (TDI increase of more than 6), but

there was no difference between this group and the placebo group. The etiology of olfactory dysfunction did not impact change in TDI in either group. Adverse effects of treatment were not discussed. Mean follow-up time was 5 months.

Minocycline

A randomized controlled study by Reden et al.⁸ from 2011 investigated the oral tetracycline class antibiotic minocycline for treatment of PVOD in 55 patients. Minocycline is typically used for acne and various other bacterial infections. Aside from having antibacterial properties, minocycline is also useful for its anti-inflammatory and neuroprotective effects, which has led to its use in Huntington's disease and various other neurological disorders. Patients

TABLE 4. List of beneficial and non-beneficial treatments for PVOD

Treatments beneficial in PVOD	Treatments not beneficial in PVOD
Oral corticosteroids	Minocycline
Local injection of corticosteroids around olfactory cleft	Vitamin A
Alpha lipoic acid	Zinc sulfate
Caroverine	<i>Ginkgo biloba</i>

PVOD = postviral olfactory dysfunction.

received minocycline at 100 mg 2 times each day for 3 weeks or placebo. The treatment group had a significant improvement in TDI of more than 6 in 15% of patients, but there was no statistical difference between the treatment and placebo groups over the 7-month follow-up time. No patients in the study reported severe adverse effects or were prevented from completing the study due to adverse effects.

Caroverine

A randomized controlled study by Quint et al.⁷ in 2002 investigated using the quinoxaline derivative caroverine to treat various sensorineural olfactory disorders, including PVOD. Caroverine and other quinoxaline derivatives are otoprotective drugs that combat glutaminergic neurotoxicity and trigger repair mechanisms in damaged units. It is sometimes used to treat tinnitus. The administered regimen included caroverine at 120 mg daily for 4 weeks vs zinc sulfate at 400 mg daily in the control group. There were 38 of 77 total patients in the study with PVOD as the etiology for olfactory dysfunction, but it is not specifically listed how many PVOD patients were in each treatment group. Olfaction was measured using BTT and Sniffin' Sticks for identification of common odors. Results showed that 13 of 35 anosmics in the treatment group improved to have measurable thresholds on BTT (6 responders had PVOD). There was no significant improvement in threshold in hyposmics or those in the zinc sulfate group suffering from anosmia or hyposmia. Identification significantly improved in anosmics (average of 5.198 points) and hyposmics (average of 5.71 points) using Sniffin' Sticks testing, but it is not listed how many of these patients had PVOD. There was no significant improvement in identification in the zinc sulfate group. Transient nausea was reported in 2 patients and transient headache in 1 patient. No severe adverse effects were reported. Follow-up time was 1 month.

Alpha lipoic acid

A prospective, noncontrolled clinical trial by Hummel et al.¹² in 2002 investigated the use of alpha lipoic acid to treat PVOD in 23 patients. Alpha lipoic acid is a nutritional supplement and antioxidant that has been used as a treatment for diabetic neuropathy. The administered regimen included alpha lipoic acid at 600 mg daily for 3 to 11 months,

over and average of 4.5 months. Of those treated, 26% showed moderate improvement in TDI (increase of at least 1.5 points but less than 5.5 points) and 35% showed remarkable improvement (TDI score increase of at least 5.5). When broken down into individual components, discrimination was significantly improved (average of 1.70 points) over baseline whereas identification and threshold improved but did not meet statistical significance. Improvement in TDI scores was more pronounced in patients under 60 years of age. Duration of symptoms was not associated with improvement. No patients in the study reported severe adverse effects or were prevented from completing the study due to adverse effects. Mean follow-up time was 4.5 months.

Zinc sulfate

A non-controlled, retrospective, parallel group trial by Aiba et al.¹⁰ from 1998 investigated the use of zinc sulfate to treat sensorineural olfactory disorders, including PVOD. There were 184 of 426 patients included in the study with PVOD. Treatment regimen included zinc sulfate at 300 mg daily for more than 1 month, zinc sulfate plus topical corticosteroids and oral vitamin B, or topical corticosteroids and vitamin B alone. The specific topical corticosteroid used was not discussed. Olfaction was tracked subjectively with questionnaires. Of those with PVOD, around 50% in each group reported subjective mild to significant improvement, but there was no statistical difference between the groups. There was no association with pretreatment serum zinc levels. Adverse effects of treatment were not discussed. Follow-up time was not clear but listed as at least 1 month.

Discussion

This systematic review of the literature over the last 48 years yielded 8 articles presenting evidence for various pharmacologic treatments of PVOD. Methods of measuring olfaction used in the studies were variable, but Sniffin' Sticks was the most common methodology used. The majority of studies included objective measures of olfaction with 1 study by Aiba et al.¹⁰ in 1998 relying solely on subjective reports by the patients. Three articles were of level 1b evidence,⁷⁻⁹ 2 articles were of level 3b evidence,^{10,11} the remaining articles were of level 4 evidence.^{5,6,12} The level 1 evidence identified consists of mostly small randomized controlled trials with 32 to 55 patients.

Of the treatment regimens reviewed, significant improvement was noted in subjects receiving oral corticosteroid therapy (level 4),⁶ local injections of corticosteroids around the olfactory cleft (level 4),⁵ alpha lipoic acid (level 4),¹² and caroverine (level 1b).⁷ The other regimens failed to show a statistically significant improvement; ie, vitamin A (level 1b),⁹ zinc sulfate (level 3),¹⁰ *Ginkgo biloba* (level 3b),¹¹ and minocycline (level 1b)⁸ (see Table 2).

Adverse effects of the reviewed treatment regimens were minimal, when reported. No severe adverse effects were

reported. Four of the included articles did not address adverse effects of treatment.^{6,9–11} Although no significant adverse effects of systemic corticosteroids were reported, the potential risks of treatment are well known to physicians and should be discussed with the patient (ie, hypothalamic-pituitary-adrenal axis suppression, hyperglycemia, gastrointestinal effects, psychiatric effects, avascular necrosis of the femoral head, osteoporosis, early cataracts, etc.).¹³ Alpha lipoic acid is similarly well tolerated in patients, but there is some small risk of hypoglycemia with use in susceptible patients.¹⁴ Minimal transient adverse effects, such as headache and nausea, were reported with caroverine use.⁷ Adverse effects of corticosteroids around the olfactory cleft have not been described.

Corticosteroid regimens used included oral prednisolone with mometasone nasal spray,¹¹ oral methylprednisolone,⁶ topical corticosteroids that were not specified,¹⁰ and local injections of dexamethasone or betamethasone into the nasal mucosa around the olfactory cleft.⁵ All of these methods yielded improvement in objective measurements of olfaction, or at least subjectively.¹⁰ Studies by Seo et al.¹¹ and Schriever et al.⁶ had grossly similar response rates of 29% with significant response with oral methylprednisolone and 32% with oral prednisolone and topical mometasone, respectively. It is difficult to compare the studies due to the different scoring systems and different corticosteroid regimens used, but there does not appear to be a significant increase in response rate when adding topical corticosteroids. The response rates reported for local injection of corticosteroids around the olfactory cleft by Fukazawa⁵ appear promising (49.6% had measureable improvement in threshold), but this study lacks clear definition of its methodology and follow-up period. Furthermore, having patients come in the office every 2 weeks for several months for corticosteroid injections may be burdensome for patients and costly for the health care system.

There is a plethora of literature on topical corticosteroids for medical treatment of rhinitis and sinusitis; however, the study by Aiba et al.¹⁰ is the only study in the literature that investigates topical corticosteroids without systemic corticosteroids as therapy for PVOD. The specific topical corticosteroid used is not mentioned and there was no objective measurement of smell. There was no difference in response rates in this study across groups receiving topical corticosteroids with vitamin B with or without zinc sulfate, or zinc sulfate alone. Thus, there is no good evidence to suggest the use of topical corticosteroids.

Comparing the results in these different studies is difficult due to the significant heterogeneity of methodology, but when taken together, this data on corticosteroids suggests that oral corticosteroids, a combination of oral and topical corticosteroids, or locally injected corticosteroids may be a reasonable treatment for PVOD, and that adding topical corticosteroids to an oral regimen may not yield much additional benefit.

Other treatments that show promise are caroverine⁷ and alpha lipoic acid.¹² Caroverine use improved olfactory

thresholds in anosmics to a measurable level but did not impact hyposmics. Identification improved in both anosmics and hyposmics as well. The level of improvement for patients with PVOD is less certain because patients with other etiologies were included in the study and response was not stratified by etiology. Though some response is possible for PVOD patients because 6 of the 13 anosmics that had improved thresholds out of the 35 patients in the treatment group had PVOD. Furthermore, our quality assessment indicates a medium risk of bias in this study and the amount of improvement is not specified—only that the olfactory threshold became detectable, and this may not translate into clinical significance. Alpha lipoic acid supplementation showed a significant improvement in olfactory discrimination in 35% without significant changes in identification or threshold. There was no control group in this study, thus spontaneous improvement cannot be ruled out. Caroverine and alpha lipoic acid may be reasonable treatments for PVOD.

Vitamin A,⁹ minocycline,⁸ and *Ginkgo biloba*¹¹ failed to demonstrate any significant improvement in the treatment of PVOD. Vitamin A and minocycline were compared to placebo in randomized controlled trials. Though neither of these regimens showed an advantage over placebo, there was significant improvement in TDI scores in 29% in the vitamin A group and 20% in the minocycline group. This suggests that a portion of people with PVOD should improve spontaneously. *Ginkgo biloba* supplementation showed a trend toward increased olfactory identification on the CCSIT when combined with oral prednisolone, but this did not reach statistical significance. Based on these results, there is no good evidence to suggest the use of vitamin A, minocycline, or *Ginkgo biloba* in the treatment of PVOD.

Zinc sulfate was administered in studies by Aiba et al.¹⁰ and Quint et al.⁷ In Aiba et al.¹⁰'s level 4 evidence study there was no difference in the subjective response rate between groups receiving zinc sulfate alone, zinc sulfate with topical corticosteroids and vitamin B, or topical corticosteroids and vitamin B without zinc. This suggests that either no treatment was not effective and improvement was spontaneous, or that zinc sulfate and topical corticosteroids are equally effective but their level of benefit does not sum when taken together. This is a poor-quality level 4 study without objective measures to determine response to treatment and the results are questionable. Another study by Quint et al.⁷ used zinc sulfate in a control group and showed that its use did not produce any significant measurable improvement in olfaction. Although small, this was a level 1b evidence study and had objective measurements of olfaction. Based on these results, there is no good evidence to suggest the use of zinc sulfate in PVOD.

It is difficult to compare many of these studies given the different methodologies and scoring systems used, but when this data is taken together a common theme emerges. Most studies report response rates around 20% to 30% regardless of the regimen. Most placebo responses fall around this

range as well. This makes any noncontrolled trial suspect to random error, as spontaneous recovery is likely to occur. Taking this into consideration, the studies that seem to stand out and show benefit with higher response rates or higher-quality data are that of Aiba et al.¹⁰ evaluating zinc sulfate (50% response rate), Quint et al.⁷ evaluating caroverine (37% response rate, though some with etiologies other than PVOD), and Fukazawa⁵ evaluating injection of corticosteroids around the olfactory cleft (49.6% response rate); though it is difficult to compare due to different definitions of what significant improvement entails. As described earlier, zinc sulfate appears to not be beneficial and Aiba et al.¹⁰'s article is level 4 evidence. Quint et al.⁷'s study on caroverine is the only randomized controlled trial showing a benefit over placebo, but the benefit in those with specifically PVOD is not clear. Fukazawa⁵'s study shows response rates near 50% when corticosteroids are injected around the olfactory cleft. Although this sounds promising, it is a level 4 study that fails to clearly describe methods and follow-up. Thus, there is no strong evidence to recommend any of the treatments reviewed. Though there is a lack of good evidence for any treatment in the literature, we feel it is still worthwhile to report these findings. It provides a basis to have an informed discussion with the patient regarding expectations of treatment.

Although the focus of this systematic review was solely on pharmacologic treatment of PVOD, there have other nonpharmacologic treatments reported in the literature. Olfactory training, for example, appears promising for treating PVOD.^{15,16} We did not review any of the nonpharmacologic treatments in the literature, thus there are other treatment options that may be available aside from what is described in this article.

Conclusion

Olfactory dysfunction is a common problem that can have significant impacts on quality of life for patients. PVOD is the most common etiology of olfactory dysfunction. Through the years numerous pharmacologic treatment regimens have been investigated. To date there is no strong evidence for any pharmacologic treatment regimen. We present the first systematic review on the medical treatment of PVOD. Oral and topical corticosteroids are likely the most commonly used regimens, but evidence of their efficacy in treating PVOD is lacking. Other treatments that show promise are caroverine, local injections of corticosteroids around the olfactory cleft, and alpha lipoic acid. Larger randomized controlled trials need to be performed to more clearly examine these regimens prior to more widespread acceptance. 

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