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Intensive Olfactory Training in Post-COVID Patients: A Randomized Multicenter Clinical Trial

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ABSTRACT

Introduction: Olfactory dysfunction (OD) is one of the most reported symptoms of COVID -19. Previous studies have identified olfactory training (OT) as an important treatment for postinfectious OD, but little is known about its effect after SARS-CoV-2 infection and how it can be optimized. **Objective**: To assess whether OT can be optimized if performed intensively, with more fragrances over a shorter period in patients with persistent OD after COVID -19. Also, to determine the presence of other variables related to OD and treatment response in this population. **Method**: This multicenter randomized clinical trial recruited 80 patients with persistent OD with previous COVID-19 for less than three months. The patients were divided into two groups, who received treatment with 4 and 8 essences over four weeks. Subjective assessments and the University of Pennsylvania Smell Identification Test (UPSIT) were performed before and after treatment. **Results**: A significant improvement in olfaction was measured subjectively and on UPSIT in both groups, but without significant differences between groups. In addition, the presence of olfactory fluctuation was associated with higher UPSIT scores. **Conclusion**: These data suggest that intensifying the training by increasing the number of essences for 4 weeks does not show superiority over the classical method. Moreover, a fluctuating olfactory ability seems to be related to a better score in the UPSIT.

Keywords: Olfactory training, anosmia, hyposmia, smell, COVID-19, coronavirus

INTRODUCTION

In December 2019, transmission of a new coronavirus (SARS-CoV-2) that causes the disease COVID -19 began in China [1]. The virus is transmitted mainly through respiratory droplets and contact routes. The most common symptoms of the disease are cough, fever, sore throat, shortness of breath, and sudden loss of smell or taste [1].

Olfactory dysfunction (OD) is now recognized as one of the cardinal symptoms of COVID-19, with a high predictive value [2]. Not only is it one of the most reported symptoms, but the magnitude of this manifestation appears to be even greater when assessed with psychophysical testing [3]. The University of Pennsylvania Smell Identification Test (UPSIT®) is a psychophysical test for the identification of microencapsulated odors that has been adapted and validated for use in different countries, including the Brazilian population [4]. Patients with COVID-19 had their UPSIT classified as anosmia or severe hyposmia in almost all cases [5].

Previous studies bring olfactory training (OT) as one of the most important treatments for postinfectious OD [6]. This therapy consists of daily and repeated exposure to odors over a long period of time [7]. Hummel et al. initially described an OT method to improve general olfactory sensitivity involving four essences (phenylethyl alcohol, eucalyptol, citronella, and eugenol), for a period of 12 weeks [8]. Altundag et at. observed that changing odors every 12 weeks can increase the success rate of this therapy in patients with post-infectious OD [7].

The current study aims to compare the response of olfactory function to OT with 4 and 8 essences in patients with recent OD post-COVID over 4 weeks. Thus, we prospectively investigated whether OT could optimize olfactory rehabilitation when it is intensive, with more fragrances, and over a shorter period. In addition, we wanted to prospectively analyze and study patients with persistent post-COVID OD to identify other variables related to the disorder or the response to OT.

METHODS

This is a multicenter randomized clinical trial involving individuals aged between 18 to 60 years with previous COVID -19 infection for less than 3 months, confirmed at that time by RT-PCR (reverse transcriptase polymerase chain reaction) testing, and complaint of olfactory alteration which persisted for at least 4 weeks after the onset of COVID -19 symptoms. Patients who were unable to provide valid written informed consent and individuals with (1) a history of more than one SARS-CoV-2 infection, (2) sinonasal diseases such as chronic rhinosinusitis or nasal masses, (3) a report of previous traumatic brain injury with olfactory sequelae, (4) OD prior to SARS-CoV-2 infection, (5) a neurologic disorder known to affect olfactory function, and (6) other current or previous treatment for OD, caused by COVID-19, were excluded from the research.

Patients were invited through the dissemination of the study in the press and social networks and followed up in the Otolaryngology services from tertiary hospitals in Curitiba and

Londrina. If the patient agreed and wanted to participate in the research, an informed consent form was applied by one of the physicians involved in the study. All participants underwent a medical examination by an otolaryngologist, which included nasal endoscopy and the application of visual analogue scales (VAS) for subjective assessment of nasal symptoms, olfaction, taste, and the effects of OD on the patient's quality of life. The presence of chemosensory disturbances, immunization against COVID-19, olfactory fluctuations, and complaints related to the nasal function of the trigeminal nerve were also assessed. Psychophysical assessment of smell was performed by the UPSIT®. This is a psychophysical and clinically validated standardized odor identification test for the "scrape and sniff" format, in which microencapsulated odorants are released from a strip when scratched. Out of a total of 40 points, normosmia is defined as ≥34 for men and ≥35 for women, and an increase of ≥4 points can be considered a clinically significant improvement in symptoms [9]. Both the UPSIT and subjective assessments were performed again within 4 weeks of starting the proposed treatment.

Patients were randomly assigned in a 2:1 ratio to two separate groups for OT. The first study group received a classical olfactory training set (COT) with four essential oils: rose, eucalyptus, clove, and lemon. The second group received an advanced olfactory training set (AOT) with eight essential oils: rose, eucalyptus, clove and lemon, citronella, mint, vanilla and cedarwood.

The guidelines for performing the OT were explained at the first appointment and provided in simple and easy-to-understand language booklets. During training, patients were exposed to each odor for 15 seconds twice daily, with a 30-second break between odors. Patients also received video instructions the day after therapy began and were contacted by telephone after completing 1 and 3 weeks of OT by the research team to emphasize the importance of treatment adherence. Along with the general instruction booklets, they were given a diary to track the training. Those who had not taken the essences for a period of at least 7 days were excluded from the study.

The study design was approved by the ethics committee of the institutions involved (CAAE: 46698721.5.0000.0096 and 47078821.5.0000.0020).

Statistical Analysis

Quantitative variables were described as mean, standard deviation, median, minimum, maximum, and interquartile range. To compare the evaluations regarding the presence of OD, the binomial test was used. A comparison between two assessments of UPSIT® and VAS scores was made using the non-parametric Wilcoxon test. Comparisons of more than two assessments were made using Friedman's non-parametric test and Dunn's post hoc test. For the comparison of two groups, concerning quantitative variables, the non-parametric Mann-Whitney test was used. More than two groups were compared using the non-parametric Kruskal-Wallis test. The analysis of the correlation between two quantitative variables was performed by estimating the Spearman correlation coefficient. To assess the association between two categorical variables, Fisher's exact test or the Chi-square test was used. Values of $p<0.05$ indicated statistical

significance. For multiple comparisons, p values were adjusted by Bonferroni correction. Data were analyzed with the computer program IBM SPSS Statistics v.28.0. Armonk, NY: IBM Corp.

RESULTS

Three hundred and forty patients were screened for eligibility, and eighty were enrolled in the study. Only one patient required intensive care during the time he had COVID-19, and the others had mild or moderate forms without requiring hospitalization. Characterization of all study participants revealed a mean age of 36.7 ± 10.3 years, a mean interval between the onset of symptoms of COVID -19 and the start of treatment with OT of 63.9 ± 24.2 days (Table 1). The mean time for the onset of OD after the onset of symptoms of COVID-19 was 4.6 ± 3.8 days. Other characteristics of the analyzed sample are shown in Table 2.

TABLE 1 – Age of participants and intervals between appointments and treatment.

	n	Mean ± standard deviation	Median (min-max.) IQR
Age (years)	80	36,7 ± 10,3	37 (18,7 – 57,7) IQR=16,1
Appointment interval (days)	80	36,1 ± 10,0	35 (21 – 78) IQR=13,5
Interval COVID-19-OT (days)	80	63,9 ± 24,2	62 (24 – 126) IQR=36,5
Olfactory dysfunction onset after COVID-19 (days)	75	4,6 ± 3,8	4 (0 – 20) IQR=5

IQR: interquartile range (quartile 3 – quartile 1); OT: Olfactory training

TABLE 2 – Description of the evaluated participants and key factors in the characterization

	Valid n	Classification	n	%
Gender	80	Female	52	65,0
		Male	28	35,0
OT Group	80	AOT	26	32,5
		COT	54	67,5
Smoking	80	Current	8	10,0
		Denied	66	82,5
		Previous	6	7,5
Hospitalization	78	No	76	97,4
		Yes	1	1,3
		Yes, ITU	1	1,3
Mechanical Ventilation during COVID-19	78	No	77	98,7
		Yes	1	1,3
Partial improvement	78	No	10	12,8
		Yes	68	87,2
Side effect with OT	80	No	62	77,5
		Yes	18	22,5
Subjective improvement	80	No	15	18,8
		Yes	65	81,3

Immunization against COVID-19	80	No	10	12,5
		Yes	70	87,5
Vaccine manufacturer	70	Astrazeneca	25	35,7
		Pfizer	25	35,7
		Coronavac	19	27,1
		Janssen	1	1,4
Vaccine before or after starting treatment	70	Before	48	68,6
		After	22	31,4

ITU: intensive treatment unit; OT: Olfactory training; AOT: Advanced Olfactory Training; COT: Classical Olfactory Training.

As seen in Table 3, the complaint of anosmia, the complete loss of the sense of smell, was reported by 82.5% of patients during the COVID -19 period, whereas it was present in only 13.8% at the time of the first appointment and was not reported by any patient after 4 weeks of OT. During the same period, the prevalence of self-reported hyposmia increased progressively. Something similar was observed for complaints of parosmia and phantosmia. Similarly, the history of ageusia was present in 63.8% of the patients in the period of COVID-19, although the prevalence decreased rapidly thereafter and was only 1.3% at the end of the study. Meanwhile, dysgeusia complaint was reported by 23.8% of patients at the time of infection, 75% at the beginning of treatment and 63.8% after 4 weeks. At the end of the study, only 3.8% of patients denied any chemosensory complaints.

TABLE 3 – Prevalence of chemosensory complaints in the initial appointment and in the return after 1 month

Classification		COVID-19		Initial Appointment		Follow-up	
		n	%	n	%	n	%
Anosmia	No	14	17,5	69	86,3	80	100,0
	Yes	66	82,5	11	13,8	0	0
Hyposmia	No	68	85,0	15	18,8	5	6,3
	Yes	12	15,0	65	81,3	75	93,8
Parosmia	No	73	91,3	54	67,5	42	52,5
	Yes	7	8,8	26	32,5	38	47,5
Cacosmia	No	75	93,8	66	82,5	66	82,5
	Yes	5	6,3	14	17,5	14	17,5
Phantosmia	No	74	92,5	59	73,8	52	65,0
	Yes	6	7,5	21	26,3	28	35,0
Dysgeusia	No	61	76,3	20	25,0	29	36,3
	Yes	19	23,8	60	75,0	51	63,8
Ageusia	No	29	36,3	74	92,5	79	98,8
	Yes	51	63,8	6	7,5	1	1,3

There was no statistically significant difference between treatment groups regarding sex, age, current or previous smoking, use of nasal corticosteroid spray, vaccination for COVID -19, the interval between onset of SARS-CoV-2 infection and treatment, and the interval between first appointment and the second visit (Tables 4 and 5).

TABLE 4 – Comparison between age and intervals between treatment groups

	Group	n	Mean ± Standard deviation	Median (min – max; IQR)	p*
Age (years)	AOT	26	38,0 ± 9,9	39,7 (20,8 – 54,7) IQR=14,9	
	COT	54	36,1 ± 10,6	36,6 (18,7 – 57,7) IQR=16,8	0,45
Interval COVID-19-OT (days)	AOT	26	61,7 ± 22,8	64 (24 – 101) IQR=36	
	COT	54	64,9 ± 25,0	62 (30 – 126) IQR=37	0,71
Appointment interval (days)	AOT	26	37,5 ± 8,8	35 (25 – 60) IQR=9	
	COT	54	35,4 ± 10,6	32 (21 – 78) IQR=13	0,13

IQR: Interquartile Range (quartile 3 – quartile 1); OT: Olfactory Training; AOT: Advanced Olfactory Training; COT: Classical Olfactory Training.

*Student's t test for independent samples or non-parametric Mann-Whitney test, p<0.05

TABLE 5 – Comparison of homogeneity of groups regarding selected key factors

Variables		Group				p*
		AOT		COT		
		n	%	n	%	
Gender	Female	19	73,1%	33	61,1%	
	Male	7	26,9%	21	38,9%	0,328
Corticosteroid nasal sprays	No	19	73,1%	42	77,8%	
	Yes	7	26,9%	12	22,2%	0,780
Smoking	Current	1	3,8%	7	13,0%	
	Denied	22	84,6%	44	81,5%	
	Previous	3	11,5%	3	5,6%	0,314
Immunization against COVID-19	No	1	3,8%	9	16,7%	
	Yes	25	96,2%	45	83,3%	0,154
Vaccine manufacturer	Pfizer	14	56,0%	11	24,4%	
	Astrazeneca	6	24,0%	19	42,2%	
	Coronavac	4	16,0%	15	33,3%	
	Janssen	1	4,0%	0	0,0%	-

*Fisher's exact test or Chi-square test, p<0.05

Participants' subjective sense of smell improved throughout the study and between medical appointments, as measured by the olfaction VAS. In the general assessment of all participants, the olfaction VAS showed a statistically significant difference in the comparison between all 4-time points at which it was assessed (before COVID-19, during COVID-19 acute phase, first appointment, and follow-up) in general comparison (non-parametric Friedman test; $p < 0.05$) and multivariate (Dunn post hoc test corrected by Bonferroni; $p < 0.05$) (Table 6). Another subjective measurement on a scale of 0 to 10 showed an improvement, the discomfort with the olfactory deficit decreased between the first and the second appointment, with a mean score of 7.2 ± 2.7 at the first appointment and 6.2 ± 3 at the second appointment ($p < 0.05$). In addition, there was a statistically significant improvement between appointments in the taste VAS scores (Table 7).

TABLE 6 – Comparison between VAS scores at separate times

Olfaction VAS	n	Mean ± Std. deviation	Median (min-max) IQR	p*
Before COVID-19	80	9,7 ± 0,7	10 (7 – 10) IQR=0	<0,001
COVID-19	80	0,9 ± 1,7	0 (0 – 7) IQR=1,5	
First appointment	80	3,6 ± 2,2	4 (0 – 8) IQR=3	
Return	80	5,8 ± 2,1	6 (0 – 10) IQR=3	

VAS: Visual analogue scale

*Friedman's non-parametric test, p<0.05

TABLE 7 – Improved taste on the Visual Analog Scale

Gustation VAS	n	Mean ± Std. deviation	Median (min-max) IQR	p*
First appointment	80	6,1 ± 2,7	6 (0 – 10) IQR=4	0,009
Second visit	80	6,9 ± 2,5	7 (1 – 10) IQR=4	
Taste improvement	80	0,8 ± 2,9	1 (-8 – 8) IQR=3,5	

VAS: Visual analogue scale

*Wilcoxon's non-parametric test, p<0.05

In the overall assessment of these participants, there was an improvement in the mean UPSIT score with a statistically significant difference when comparing the initial (25.2 ± 7.1) and final (26.7 ± 6.3) UPSIT, a mean increase of 1.5 ± 3.9 in the final test score (Wilcoxon nonparametric test; p=0.002). When comparing between the COT and AOT groups, UPSIT and olfaction VAS were examined, but none showed a significant difference between the different treatment groups (Table 8). When comparing the outcome of the directly queried subjective improvement, where only yes or no responses were possible, 81.3% of participants reported improvement, but there was no statistically significant difference between treatment groups.

TABLE 8 – Comparison of objective and subjective variables that assess olfactory function between treatment groups

	Group	**n**	**Mean ± Std. deviation**	**Median (min-max) IQR**	**p***
Initial UPSIT	AOT	26	26,2 ± 6,1	27,5 (15 – 34) IQR=11	
	COT	54	24,7 ± 7,5	25,5 (5 – 36) IQR=9	0,481
Final UPSIT	AOT	26	27,2 ± 4,8	27 (15 – 35) IQR=6	
	COT	54	26,4 ± 6,9	28,5 (10 – 38) IQR=9	0,992
UPSIT score improvement	AOT	26	1,0 ± 4,2	1 (-7 – 10) IQR=4	
	COT	54	1,7 ± 3,8	2 (-7 – 12) IQR=5	0,281
Olfaction VAS before COVID-19	AOT	26	9,6 ± 0,7	10 (8 – 10) IQR=1	
	COT	54	9,7 ± 0,7	10 (7 – 10) IQR=0	0,508
Olfaction VAS in COVID-19	AOT	26	1,0 ± 1,9	0 (0 – 7) IQR=1	
	COT	54	0,9 ± 1,5	0 (0 – 5) IQR=2	0,761
Olfaction VAS at initial appointment	AOT	26	3,8 ± 1,5	4 (1 – 8) IQR=1	
	COT	54	3,5 ± 2,5	3 (0 – 7) IQR=5	0,471
Gustation VAS at initial appointment	AOT	26	6,0 ± 2,4	6 (2 – 10) IQR=4	

	COT	54	6,2 ± 2,8	6 (0 – 10) IQR=3	0,608
Annoyance with the OD at initial appointment	AOT	26	7,9 ± 2,4	9 (0 – 10) IQR=4	
	COT	54	6,8 ± 2,8	7 (1 – 10) IQR=5	0,122
Nasal symptoms at initial appointment	AOT	26	4,7 ± 3,4	6 (0 – 10) IQR=7	
	COT	54	4,1 ± 3,4	3 (0 – 10) IQR=6	0,548
Olfaction VAS at return	AOT	26	5,6 ± 2,2	6 (0 – 10) IQR=3	
	COT	54	5,8 ± 2,1	6 (0 – 9) IQR=3	0,499
Gustation VAS at return	AOT	26	7,2 ± 2,2	7,5 (2 – 10) IQR=3	
	COT	54	6,8 ± 2,7	7 (1 – 10) IQR=4	0,655
Annoyance with the OD at return	AOT	26	6,5 ± 2,8	6,5 (0 – 10) IQR=4	
	COT	54	6,0 ± 3,1	7 (0 – 10) IQR=6	0,609
Nasal symptoms at return	AOT	26	4,3 ± 3,2	5 (0 – 10) IQR=7	
	COT	54	4,4 ± 3,4	5 (0 – 10) IQR=6	0,872
Gustation improvement (VAS)	AOT	26	1,2 ± 2,9	1 (-6 – 6) IQR=4	
	COT	54	0,6 ± 2,9	1 (-8 – 8) IQR=3	0,491
Improved sense of smell (VAS)	AOT	26	1,8 ± 2,3	2 (-4 – 7) IQR=3	
	COT	54	2,4 ± 2,3	2 (-5 – 7) IQR=3	0,254
Annoyance improvement (VAS)	AOT	26	-1,3 ± 2,9	-1 (-8 – 6) IQR=3	
	COT	54	-0,8 ± 3,4	-1 (-10– 7) IQR=3	0,384
Nasal symptoms improvement (VAS)	AOT	26	-0,3 ± 3,2	0 (-6 – 7) IQR=4	
	COT	54	0,3 ± 4,7	0 (-10 – 8) IQR=5	0,244

UPSIT: University of Pennsylvania Smell Identification Test; VAS: Visual analogue scale; COT: Classical Olfactory Training; AOT: Advanced Olfactory Training; OD: Olfactory Dysfunction.
*Mann-Whitney non-parametric test, p<0.05

In relation to other measured factors that could be related to the outcomes of olfaction, it was observed that patients who reported fluctuations in their olfactory ability at the initial appointment (Mann-Whitney nonparametric test) had higher UPSIT scores at baseline (26.8 ± 6.1 vs. 22.3 ± 7.9; p=0.011) and at final presentation (28.1 ± 4.8 vs. 24.0 ± 7.6; p=0.029) compared with participants who did not report this symptom. In addition, these patients with fluctuating olfaction had more nasal symptoms at the first visit (5.2 ± 3.4 vs. 2.9 ± 3.0) than patients without this symptom (p=0.003). Nevertheless, subjective improvement, as measured by olfaction VAS was statistically lower in these patients (1.8 ± 2.5 vs. 2.9 ± 1; p=0.03). The smell fluctuation differed between the first visit and return (binomial test; p=0.023). At the first assessment, 62.8% of patients reported this symptom; at the return, 78.8% reported it.

There was no association between the reported changes in nasal functions of the trigeminal nerve and the presence of any of the chemosensory disorders in any of the moments evaluated (Fisher's exact test, $p < 0.05$). We also found no association between these complaints and the mean of the UPSIT scores or the applied VAS (nonparametric Mann-Whitney test, $p < 0.05$).

DISCUSSION

To date, there have been few randomized clinical trials involving olfactory training in patients with OD associated with COVID-19, and no study has yet compared variants of this therapy in this subset of patients. In addition, this is the first study to evaluate an alternative method for OT in patients with OD using eight concurrent essential oils. Another highlight of our study was the complete evaluation of patients by an otolaryngologist, including nasal endoscopy and the use of a psychophysical test that has been validated for the studied population and is widely used in research on the sense of smell. Several associated factors that might be related to olfactory complaints or response to therapy were also controlled, such as age, smoking history, duration of the olfactory dysfunction, qualification of the disorder, smell fluctuations, report of impaired trigeminal function, OT adherence, nasosinusal symptoms, and use of topical corticosteroids. Patients also received explanatory videos of the OT on their smartphones and were contacted by telephone to ensure adherence.

The selection of AOT essential oils was made by a fragrance expert in our research group based on olfactory training methods used for training recognition and memorization of odors, such as the Carles Method [10]. We sought to cover different families of odors to improve training by enhancing the receptors activated in therapy. In addition to lemon, rose, eucalyptus, and clove, representatives of the citrus, floral, aromatic, and spice families, minty, sweet, and woody odors were added with essential oils of citronella, mint, vanilla, and cedarwood. We hoped that adding more scents to OT would optimize olfactory recovery in patients. However, no statistical difference was found in the UPSIT score progression between the AOT (1.0 ± 4.2) and COT groups (1.7 ± 3.8) of the study (p=0.281). Similarly, no differences were found between the groups in the data collected via the various VAS-scores (Table 8). The data suggest that OT intensification does not show superiority over classical training during the 4-week period proposed in this study.

In a study conducted by Altundag et al., a modified form of OT was assessed in which patients trained four different essences every 12 weeks over a 36-week period. It was found that the group that performed such alternation scored better on the Sniffin' Sticks test than the group that performed the classical 4-essence OT [7]. It was also found that the shorter the duration of the loss of smell, the better the response to the OT. This correlation has also been observed in several other papers [11–13]. In our study, we sought to include only patients with recent OD, to maximize the potential benefit of training and to improve the analysis of differences between groups. However, a major difference between our work and that of Altundag et. al. concerns the period of use of OT, which is significantly shorter in our study and probably related to the lack of benefit of the AOT group.

In a clinical study comparing periodic alternation of odors with classical training in patients with posttraumatic OD, no significant difference was found between the training modalities [14]. We know that olfactory rehabilitation by OT shows different results depending on the etiology of the dysfunction. Patients with posttraumatic etiology respond worse than patients with postinfectious OD, for example [11]. To date, no study has examined the efficacy of modified OT in patients after COVID 19.

Another challenge to the analysis and applicability of treatments for OD is OT adherence [6]. As described by Fornazieri et al, adherence to treatment progressively decreases over the months of treatment [15]. In light of this, the possibility of intensifying OT by increasing the number of scents for a shorter treatment duration has been suggested. At the end of the survey, only 3.75% of patients had discontinued treatment, one in the AOT group and two in the TOC group. Regarding daily adherence, none of the patients failed to use the OT for 7 days, so there was no exclusion based on this criterion. The occurrence of side effects was limited to mild symptoms without the need to interrupt the OT. The most commonly reported complaints were headache, nausea and worsening of nasal symptoms.

Another important analysis concerns self-assessment and performance in psychophysical tests. In our study, 81.3% of participants reported that their sense of smell improved, 84.6% in the AOT group and 79.6% in the COT group (p=0.763). Considering all groups, the increase in mean UPSIT score was 1.5 ± 3.9 points (p=0.002). Changes to UPSIT of four or more points can be considered as a clinically relevant improvement [16,17], but this difference was observed in only a few patients in the study. The weak association between these tests and subjective assessment has been described in some previous papers [18–21], which underlines the importance of assessing patients with olfactory complaints with standardized tests in addition to self-assessment.

The average time reported for the onset of OD (Table 1) after the onset of symptoms of COVID -19 was 4.6 ± 3.8 days, which is consistent with what has been reported in the literature [22,23].

Several studies have shown that COVID -19-related OD has a short recovery period in most patients, occurring on average 1 to 2 weeks after the onset of the disorder [22,24–26]. In a paper by Vaira et al, a higher risk for a long-lasting olfactory disturbance was observed in patients in whom symptoms persisted 20 days after the onset of OD [25]. In our study, all patients were selected after at least 4 weeks of olfactory complaints to reduce those who would show spontaneous recovery regardless of therapy.

In the present study, similar to the literature, a sudden anosmia was observed in the acute state of COVID -19 (Table 3), leading to a progressive recovery that was accompanied by the appearance of other qualitative disorders of olfaction [27]. Although parosmia seems to be indicative of the recovery of the functions of olfactory discrimination and identification [28], we could not find any relationship between the presence of this symptom and a better development by UPSIT or by the olfaction VAS.

In the global analysis of patients by gustation VAS (Table 7), mean values of 6.1 ± 2.7 and 6.9 ± 2.5 were obtained at the first and second appointments, respectively, corresponding to an improvement of 0.8 ± 2.9 (p=0.009). However, the data showed no statistical difference between the groups of OT (Table 8), neither in the mean of the first appointment (p=0.608) nor in the difference between it and the mean of the return (p=0.491).

Patients were asked about their perception of fluctuations in their sense of smell during both assessments. At baseline, these complaints occurred in 62.8% of patients and at the end in 78.8%, a more marked prevalence than that reported by Jerome et. al [29]. As expected, patients

with fluctuations in olfaction also had higher VAS scores for nasal symptoms (p=0.003). Fluctuations in olfaction are commonly associated with nasal conditions, such as allergic diseases [30] and are less pronounced in patients with postinfectious OD [31].

The presence of this symptom at the first appointment was associated with better scores at both the first UPSIT (p=0.011) and the second appointment (p=0.029). These results may suggest that the fluctuations are also related to the regeneration of the neuroepithelium.

Interestingly, olfactory fluctuations were related to worse smell evolution measured by VAS (p=0.029). Considering that self-assessment of this sense seems to reflect mainly changes in nasal patency and, to a lesser extent, olfactory function [32], this would explain why fluctuations in our study were more pronounced in patients with more severe nasal symptoms, who therefore reported worse VAS.

The trigeminal nerve has an important influence on olfactory perception, being associated with the sensation of freshness for minty odors and the tickling sensation for carbonated beverages [33]. Its somatosensory function in the nose was assessed using standardized questions during the history at initial presentation. The relationship between trigeminal function impairment and reported chemosensory disturbances at three time points was assessed: the acute period of SARS-CoV-2 infection; the first appointment; the return. None of the reported disturbances were found to be related to trigeminal function, suggesting a pathophysiology likely distinct from that of olfaction.

The main limitation of the present study is the short duration of the proposed treatment. The aim is to evaluate an alternative to the TOC originally described by Hummel et. al [8], that is performed intensively, including twice as many scents, and with fewer weeks of stimulation. We are aware that most of the studies conducted on this topic have maintained olfactory training for a longer period, which limits our analysis of the potential benefits of AOT.

Another possible criticism relates to the psychophysical test chosen to assess patients, as the UPSIT limits the assessment to odor identification only and does not take into account the discrimination or olfactory threshold abilities present in other tests. However, work conducted by Doty et al. suggested that different psychophysical tests measure what would be a common source of variation, so that olfactory impairment and improvement can be effectively assessed using only the identification of odors [34].

CONCLUSION

Prospective evaluation with subjective scales and psychophysical tests in patients with persistent olfactory dysfunction post-COVID showed an improvement in the smell capacity with the OT performed during 4 weeks. However, the data suggest that intensifying the training by increasing the number of essences does not show superiority over the four-week classical method. Future studies with an extension of the treatment period are needed to analyze AOT's potential benefits better. Additionally, the data indicate that patients with fluctuating olfactory ability have better scores in the psychophysical assessment.

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César Antônio Veiga works for O BOTICÁRIO FRANCHISING LTDA. The other authors have no conflicting interests to declare.

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