Original Article

American Journal of Rhinology & Allergy
2020, Vol. 34(2) 238–248

DOI: 10.1177/1945892419887895
journals.sagepub.com/home/ajr
SAGE

Adherence and Efficacy of Olfactory Training as a Treatment for Persistent Olfactory Loss

Marco Aurélio Fornazieri, MD, PhD[1,2,3,4], Ellen Cristine Duarte Garcia, MSc[1], Natália Medeiros Dias Lopes, MSc[1], Isabela Naomi Iha Miyazawa[1], Gislene dos Santos Silva[1], Rebeca dos Santos Monteiro[1], Fábio de Rezende Pinna, MD, PhD[3], Richard Louis Voegels, MD, PhD[3], and Richard L. Doty, PhD[4]

Abstract

Background: Among emerging therapies, olfactory training (OT) has been proposed as a potential treatment for persistent olfactory loss. This treatment has been suggested to improve olfactory function via sensorineural modulation from repeated odor exposure. However, due to the long treatment period that is required, many patients discontinue the treatment or do not follow the treatment regimen appropriately, potentially biasing estimates of treatment success. Moreover, spontaneous improvement is known to occur without any interventions.

Objectives: We evaluated both the adherence rates and the efficacy of OT in patients with persistent postinfectious, posttraumatic, or idiopathic olfactory loss.

Methods: Prospective observational study. Twenty-five patients with persistent olfactory loss underwent OT. Protocol adherence and olfactory function (scores on the University of Pennsylvania Smell Identification Test or UPSIT) were assessed 3 and 6 months after the initiation of treatment. A minimum improvement of 5 UPSIT points was considered clinically significant and adherence throughout the study.

Results: The adherence rate of the patients after 3 months was 88% and after 6 months was 56%. The corresponding percentages of clinical improvement were 23.5% and 25%. There was no relation of age, sex, time of olfactory loss, race, the degree of olfactory loss, etiology, education, and type of training to the adherence rate or treatment efficacy.

Conclusions: In this patient population, adherence to training remained high in the first 3 months of OT but declined moderately thereafter. The observed prevalence and degree of improvement were similar to that reported a number of studies, including some studies whose patients did not receive OT.

Keywords

olfaction, olfactory disorders, olfactory test, smell, smell tests, UPSIT, olfactory epithelium, adherence, training, olfactory training

Introduction

Olfactory dysfunction afflicts about 20% of the population.[1] People deprived of normal olfaction have difficulty in performing daily activities such as cooking and evaluating their hygiene. They also become more susceptible to depression, accidents due to domestic gas leaks, and food poisoning.[2–4] Upper respiratory tract infections, cranial traumas, and inflammatory and obstructive nasal diseases constitute 60% of the etiologies in

[1]Department of Clinical Surgery, Londrina State University, Londrina, Brazil
[2]Department of Medicine, Pontifical Catholic University of Paraná, Curitiba, Brazil
[3]Department of Otolaryngology, University of São Paulo, São Paulo, Brazil
[4]Smell and Taste Center, Department of Otorhinolaryngology—Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Corresponding Author:
Marco Aurélio Fornazieri, Department of Clinical Surgery, Londrina State University, 60 Robert Koch Avenue, 86038350 Londrina, PR, Brazil.
Email: marcofornazieri@uel.br

patients with this disorder.[3] Other common causes are presbyosmia—olfactory loss due to aging[5–8]—and neurodegenerative diseases such as Parkinson's and Alzheimer's.[9,10]

To date, there are no well-established and agreed-upon effective treatments for olfactory disorders, except some surgical operations for tumors and corticosteroid treatments for allergies and nasal inflammatory diseases. It is well known that the olfactory epithelium, along with some other elements of the olfactory pathways, has some capacity for regeneration.[11,12] Relying, in large part, on this fact is the recent proposal that olfactory function can be improved in patients with persistent olfactory loss by having them sniff a series of odorants on a daily basis over the course of a number of months, a process called olfactory training (OT).[13]

The first clinical study to employ OT reported that olfactory function significantly improved in 28% of patients with posttraumatic, postinfectious, or idiopathic olfactory deficits after 12 weeks of therapy. Subsequent clinical studies, using the same treatment for 16 to 18 weeks, have reported, on average, improvement in 37.8% of patients with postinfectious loss and in 33.2% of patients with posttraumatic loss.[14,15] In Parkinson's patients, 20% were reported to significantly improve following OT.[15] It is noteworthy that, in a number of studies, training was effective regardless of the duration of the loss, gender, age, and severity of the dysfunction.[14–16] Additional data on the OT efficacy and adherence in patients with postinfectious, posttraumatic, and idiopathic olfactory loss are shown in Table 1.

Regardless of such findings, however, it should be noted that the degree of improvement in such studies is often no more than that reported in longitudinal studies of nontreated patients with similar dysfunctions. Hendriks reported spontaneous recovery in 36% of patients over a period of about a year.[27] Duncan and Seiden noted that 67% of 21 patients with postinfectious olfactory dysfunction, followed for an average of 37 months, significantly improved their scores on the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT).[28] London et al. found, in a study of 542 patients, statistically significant improvement in UPSIT scores for 57% of the anosmic and 42% of the hyposmic patients over an average 3.5-year period.[29] Unlike a number of other studies, the amount of change was related to age, severity of initial olfactory loss, and the duration of dysfunction at the time of the first test, but not to sex, etiology, smoking behavior, and the time between the 2 test sessions. Importantly, only 11% of the anosmic and 23% of the microsmic patients regained normal age-related function as per UPSIT norms.[30]

As presently conceived, OT is a long-term therapy, and its results take weeks or months to be perceived by patients. Aside from the fact that nonodor control groups are lacking in the studies on this topic, only a few studies have shown the rate of, or reasons for, discontinuance in patients who begin this therapy.[14,15,24] Such information could be of clinical value in helping patients to maintain compliance over the prolonged periods dictated by the therapy.

This study evaluated the efficacy and the adherence to OT in a population of patients experiencing persistent postinfectious, posttraumatic, or idiopathic olfactory loss. A preliminary assessment was made in our relatively small sample as to whether treatment efficacy and adherence was influenced by factors such as age, sex, race, time of olfactory loss, the degree of olfactory loss, etiology, schooling, odorant exposure types, and the presence of parosmia (odor distortion) or phantosmia (olfactory sensation in the absence of a stimulus).

Material and Methods

Patients

Twenty-five patients, ranging in age from 22 to 82 years, were recruited from 2 smell and taste centers from January 2015 to December 2018. The olfactory deficits in 13 were due to upper airway infections and in 6 were due to head trauma. Six patients were classified as idiopathic, that is, having an etiology that could not be established from a detailed history or magnetic resonance imaging. The other clinical and sociodemographic characteristics of the patients and their initial UPSIT scores are shown in Table 2. The median duration of smell loss for posttraumatic smell loss patients was 2.5 years (interquartile range [IQR]: 2–1), for postinfectious was 1 year (IQR: 2–0.2), and for idiopathic was 1.8 years (IQR: 2–0.4). All the patients underwent nasal endoscopy, and none of them exhibited obstructive septal deviations, polyps, or yellowish secretions which would indicate chronic rhinosinusitis or would prevent odorants from reaching the olfactory epithelium. None of the participants were smokers. The study was approved by the local ethics committee and all patients signed the informed consent.

Olfactory Training

OT consisted of the patients smelling different odors for 10 seconds each, twice a day for 6 months. Twelve patients—3 idiopathic, 8 postinfectious, and 1 posttraumatic, median duration of smell loss: 0.7 years (IQR: 2.5–0.2)—received a box containing 4 bottles containing 1 mL of the following essences: phenyl ethyl alcohol, eugenol, citronellal, and eucalyptol (classical training). Patients received new bottles in the third month. The second group with 13 patients—3 idiopathic, 5

Table 1. Specifics of Prior Studies Related to Efficacy and Adherence to Olfactory Training Regimens in Patients With Olfactory Dysfunction Due to Various Etiologies.[13–26]

Study	Study Design	Mean (SD) Age	Cause of Olfactory Loss	Type of Training	Test	Measure of Effectiveness	Percentage of Patients With Significant Improvement (Period of Training)	Percentage of Patients Who Stopped OT (Reasons for Stopping)
Hummel et al.[13]	Prospective study; 40 patients received OT and 16 were controls	57.8 (12.0)	Postinfectious, posttraumatic or idiopathic	Patients exposed twice daily to PEA, eugenol, eucalyptol, citronellal	SS	Improvement of TDI score $\geq$6	28% in the training group and 6% in the controls (12 weeks)	Not described
Fleiner et al.[17]	Retrospective; 28 patients received OT and 18 received OT + topical corticosteroids	59.2 (13.3)	Sinonasal, postinfectious, posttraumatic, and idiopathic	OT for 10 seconds twice daily with 4 different odors among rose, orange, citrus, peppermint, raspberry, chocolate, vanilla, cinnamon, and leather	SS	Improvement of TDI score $\geq$6	10.7% in the training-only group; steroid + training, 33% improved (35 weeks)	17.8% lost follow-up, reasons were not described
Haehner et al.[16]	Prospective, controlled, nonblinded; 35 PD patients and 35 controls	Range: 43–76	Parkinson's disease	Similar to Hummel et al.[13]	SS	Improvement of TDI score $\geq$5.5	20% in the training group and 9% in the controls (12 weeks)	Not described
Konstantinidis et al.[14]	Prospective study; 72 patients were allocated to do the OT and 47 were controls	48.9 (9.2)	Postinfectious (49 OT, 32 C) and posttraumatic (23 OT, 15 C)	Similar to Hummel et al.[13]	SS	Improvement of TDI score $\geq$6	67.8% of postinfectious and 33.2% of posttraumatic patients (16 weeks)	4% stopped training (no perceived benefit, nose irritation or headache after OT)
Damm et al.[15]	Randomized, investigator-blinded, cross-over study; 70 trained with high concentrations of 4 odors for 18 weeks; 74 with low concentrations of odors. Cross-over at 18 weeks	54.6 (9.6)	Postinfectious olfactory dysfunction of $<$24 months	Patients exposed twice daily to PEA, eugenol, eucalyptol, citronellal at low (0.0001%) or high (neat) concentrations	SS	Improvement of TDI score $\geq$6	High training group 26% and low-training group 15% (18 weeks). Low–high training group 30.8% and the high–low training group 45.8% (36 weeks)	Not described

(continued)

Table 1. Continued

Study	Study Design	Mean (SD) Age	Cause of Olfactory Loss	Type of Training	Test	Measure of Effectiveness	Percentage of Patients With Significant Improvement (Period of Training)	Percentage of Patients Who Stopped OT (Reasons for Stopping)
Geißler et al.[18]	Prospective non-randomized clinical study. All patients did the same type of OT	56 (8)	Postinfectious olfactory dysfunction <24 months	Similar to Hummel et al.,[13] but SS pens with same OT substances instead of bottles	SS	Improvement of TDI score ≥2	79% (32 weeks)	All patients completed the training period
Schriever et al.[19]	Prospective study to examine the effect of OT in older people; 43 participants performed the training and 48 were controls	81 (8.6)	Volunteers with probable olfactory dysfunction related to age	They were instructed to smell citronellal, cineol, eugenol, and PEA for 30 seconds twice daily	SS	Statistically significant change in means of the test	No significant change	48% of the participants in the training groups did not follow the protocol as requested
Kollndorfer et al.[20]	Prospective study. All patients were instructed to expose themselves twice a day to each of the 4 odors and take 1 deep sniff of every odor	41.6 (12.9)	Postinfectious olfactory dysfunction (all patients with anosmia)	Participants had to choose 4 of 6 odors to perform the OT: cinnamon, vanilla, orange, rose, menthol and banana	SS	Total test score difference	No total score mean difference (before 11.82 ± 1.66, after 13.79 ± 4.21, $P = .128$); threshold improved in 6 out 7 patients (before 1.39 ± 0.61, after 3.07 ± 1.98; 12 weeks)	4 anosmic patients did not complete the tests, no reasons were mentioned
Altundag et al.[21]	Prospective study; 37 patients used a modified OT, 33 the original one similar to Hummel et al.,[13] and 15 were controls	45.6 (10.5)	Postinfectious olfactory dysfunction	Patients exposed themselves twice daily to 4 odors for 10 seconds each during 5 minutes, with time intervals of 10 seconds between odors	SS	Improvement of TDI score ≥6	MOT = 56%, classical OT = 46%, C = not described (24 weeks); MOT = 56%, classical OT = 46%, C = not described (36 weeks)	Not described
Konstantinidis et al.[22]	Prospective study; 36 patients trained for 16 weeks, 34 for 56	62.9 (6.2)	Postinfectious olfactory dysfunction	Exposure to odorants similar to Hummel	SS	Improvement of TDI score ≥6	Long-term group- = 71%, short-term = 58%,	5 OT subjects discontinued (3 from nose

(continued)

Table 1. Continued

Study	Study Design	Mean (SD) Age	Cause of Olfactory Loss	Type of Training	Test	Measure of Effectiveness	Percentage of Patients With Significant Improvement (Period of Training)	Percentage of Patients Who Stopped OT (Reasons for Stopping)
	weeks and 41 were controls			et al.[13] in 2 sessions of 5 minutes			C = 37% (56 weeks)	irritation and headache; 2 because of long treatment period)
Poletti et al.[22]	Prospective study; 48 patients performed OT with odors containing heavy-weight molecules and other 48 with low-weight molecules	59.4 (12.6)	Posttraumatic and postinfectious olfactory dysfunction	Three different odors in brown glass jars were smelled for 10 seconds twice a day	SS	Improvement of TDI score ≥5.5	Postinfectious olfactory dysfunction = 45% and posttraumatic = 16% (5 months); 36% with LWM and 38% in patients trained with HWM (5 months)	Not described
Patel et al.[24]	Randomized controlled trial; 19 patients received the OT and 16 were controls	56 (range: 39–71)	Postinfectious and idiopathic with smell loss greater than 1 year of duration	Instructed to obtain essential oil containers (rose, lemon, eucalyptus, and clove) and breathe contents, slowly and deeply, for 15 seconds, twice a day	UPSIT	10% improvement compared to the first test	OT = 32% and C = 13% (6 months)	One patient stopped the training, no reason reported
Nguyen and Patel[25]	Randomized controlled trial; 138 patients with olfactory loss and without any inflammatory signs at nasal endoscopy; randomized to OT or OT plus budesonide irrigation	56.3 (14.7)	Postinfectious, medication-related, traumatic, environmental exposure, or idiopathic	Similar to Patel et al.[24]	UPSIT	Improvement of UPSIT score ≥5.5	OT = 26.9% and OT plus irrigation = 43.9% (6 months)	Not described

(continued)

Table 1. Continued

Study	Study Design	Mean (SD) Age	Cause of Olfactory Loss	Type of Training	Test	Measure of Effectiveness	Percentage of Patients With Significant Improvement (Period of Training)	Percentage of Patients Who Stopped OT (Reasons for Stopping)
Langdon et al.[26]	Prospective, randomized, controlled study; 21 patients did the training and 21 were controls	34	Posttraumatic	Twelve weeks performing twice daily with a 6 odor training set	BAST 24; butanol threshold	Improvement of 30% in any of the tests	Threshold test: OT = 26% and C = 5%; BAST 24: OT = 62% and C = 38% (12 weeks)	Not described

Abbreviations: BAST, Barcelona Smell Test; C, controls; HWM, heavy weight molecules; LWM, low-weight molecules; MOT, modified olfactory training; OT, patients doing olfactory training; PEA, phenyl ethyl alcohol; SS, Sniffin' Sticks test; TDI, threshold-discrimination-identification; UPSIT, University of Pennsylvania Smell Identification Test.

postinfectious, and 5 posttraumatic, median duration of smell loss: 1.5 years (IQR: 3–1)—used odors of commercial products from previously determined brands found in grocery stores (modified training). They were the coffee powder (2 tablespoons), vanilla essence (Dr Oetker), cloves (10), toothpaste (Colgate® Natural, 20 g), grape vinegar (Castelo®, 20 mL), honey (20 mL), and mandarin juice (Maguary®, 20 mL). The patients in this group were instructed to change the products every week. During the OT orientation, we told all patients the need for therapy constancy and informed them of the possibility that olfactory improvement may take many months after the initiation of the OT. In addition, monthly phone calls were made to patients to increase adherence to the treatment regimen.

Efficacy and Adherence to OT

The efficacy of treatment was considered clinically significant if the patient exhibited a 5-point increase (12.5% of the total test score) or higher on the UPSIT at 3 or 6 months after the start of the training. The UPSIT consists of 4 booklets of 10 odors each, with 1 different smell on each page. The stimuli are encapsulated in plastic microcapsules present in a label at the bottom of each page. The examiner advises the patient to scratch the label with a pencil, which releases the odor. After this, the patient places the scratched label 1 to 2 cm near the nose and indicates which of 4 words best represents the perceived smell. The testing is forced-choice, that is, requires a response. Based on the number of correct items and validated scores for the local population, the patient's olfactory function was classified as normal (above 31 in men and above 34 in women), microsmic (between 17 and 31 in men and 19 and 34 in women), and anosmic (less than 17 in men and 19 in women).[31]

We evaluated the adherence during the third- and sixth-month visits. When the patient failed to return to the clinic, we contacted them by telephone. All patients were asked about any adverse effects on the 2 test occasions and, if withdrawal occurred, the reason for the withdrawal. Efficacy was determined only for the patients who completed the treatment in each test period. Lack of adherence was defined when the patient did not follow the protocol as requested or stopped training during the period of the study.

Statistical Analysis

Continuous variables were described as means and their respective standard deviations and categorical variables in percentages. The olfactory test scores were compared between visits by repeated measures analysis of variance. Comparisons of adherence rates and efficacy among sexes, age groups, races, educational levels, different

Table 2. Initial UPSIT Scores According to Socioeconomic and Clinical Data.

			Pretreatment UPSIT Scores				
Variables	Categories	Sample Size	Mean	SD	Median	Min	Max
Sex	Men	8	11.9	6.8	12.0	1	24
	Women	17	16.2	5.9	13.0	7	27
Age	<55 years	11	14.1	4.3	13.0	9	23
	≥55 years	14	15.7	7.8	13.0	1	27
Race	White	19	16.2	5.9	13.0	7	27
	Non-White	6	11.3	6.8	11.5	1	22
Education	<High school	9	13.8	6.7	12.0	7	27
	High school	3	15.5	3.5	15.5	13	18
	Bachelors or higher	13	15.7	6.7	13.0	1	24
Degree of loss	Anosmia	17	11.2	3.6	12.0	1	18
	Microsmia	8	22.5	2.7	22.5	19	27
Etiology	Posttraumatic	6	13.2	3.3	13.0	9	19
	Postinfectious	13	15.1	7.2	13.0	1	27
	Idiopathic	6	16.8	7.1	19.0	7	24
Type of training	Modified	13	14.8	5.3	13.0	7	24
	Classical	12	15.1	7.7	13.0	1	27
Parosmia	No	12	14.3	7.2	12.0	1	24
	Yes	5	16.8	6.7	19.0	7	23

Abbreviation: UPSIT, University of Pennsylvania Smell Identification Test.

times of olfactory loss, degrees of olfactory loss, etiologies, types of training, presence or absence of parosmia and phantosmia in some moment after the start of the olfactory deficit was performed by the Fisher exact test, considering a statistically significant result when $P < .05$. Based upon power analyses, a sample size of 12 participants was found adequate to detect a 5-point mean change in UPSIT score at an alpha level of 5% with the power of 80% assuming a 4-point standard deviation.[29,32]

Results

Adherence to OT

After 3 months, 22 of the 25 study patients (88%) continued, while 3 (12%) abandoned the treatment. By the sixth month, adherence was 56% (14 patients), and the discontinuation rate was 44%. The reason cited for all who discontinued therapy was the absence of noticeable improvement in the ability to smell. As observed in Table 3, there was a nonsignificant tendency for more men than women to adhere to the treatment by the end of the sixth-month period. Age, time of olfactory loss, race, schooling, the degree of olfactory loss, etiology, type of training, and the presence of phantosmia or parosmia did not appear to be related to the adherence to treatment at either time period, although definitive assessment of such variables would require a larger sample size.

Efficacy of OT

From the 17 patients who continued training until the end of the third month and repeated the olfactory test at this time, 4 (23.5%) had clinically significant improvement. In the sixth month, the efficacy of OT was 25% (Figure 1). One of the patients who had improved initially worsened again (initial UPSIT = 13 points, after 3 months = 21 points, at 6 months = 17 points). Eighty-one percent of the initial anosmic patients continued to be anosmic, and 18.8% became microsmic; 87.5% of the initial microsmic group continued microsmic, and 12.5% worsened to anosmia. As shown in Table 4, the treatment appeared to be marginally better in those who used the classical compared to the modified training regimen ($P = .04$). No association with the efficacy of the training with the other variables analyzed was observed in the third and the sixth months. During follow-up, none of the patients reported side effects.

Discussion

In this study, in addition to efficacy, we examined the prevalence of adherence to the protocol and, for the first time, motives as to why patients with olfactory loss discontinued OT. In addition, we compared classical OT based on 4 odors[13] to an OT based upon practice stimuli comprised of standardized products available in grocery stores. The new scents added in the modified modality, such as vinegar and honey, are not composed of neat molecules as in the classical form, but of a mixture of

Table 3. Relationships Between Demographic Factors and Other Variables With the Adherence on the Third and Sixth Months After the Beginning of Olfactory Training.

Variables	Categories	Adherence in the Third Month n (%)	*P*	Adherence in the Sixth Month n (%)	*P*
Sex	Men	7/8 (87.5)	1.0	7/8 (87.5)	.08
	Women	15/17(88.2)		8/17 (47.1)	
Age	<55 years	10/11 (90.9)	1.0	5/11 (45.4)	.24
	≥55 years	12/14 (85.7)		10/14 (64.2)	
Race	White	16/19 (84.2)	.55	11/19 (52.6)	1.0
	Non-White	6/6 (100.0)		4/6 (66.6)	
Education	<High school	8/9 (88.8)	1.0	4/9 (44.4)	.27
	High school	3/3 (100.0)		3/3 (100.0)	
	Bachelors or higher	11/13 (84.6)		8/13 (53.8)	
Degree of loss	Anosmia	14/17 (82.4)	.53	10/17 (58.8)	1.0
	Microsmia	8/8 (100.0)		5/8 (62.5)	
Etiology	Posttraumatic	6/6 (100.0)	1.0	5/6 (83.3)	.33
	Postinfectious	11/13 (84.6)		6/13 (46.2)	
	Idiopathic	5/6 (83.3)		4/6 (66.6)	
Type of training	Modified	12/13 (92.3)	.59	8/13 (61.5)	1.0
	Classical	10/12 (83.3)		7/12 (58.3)	
Phantosmia	No	11/14 (78.6)	1.0	8/14 (57.1)	1.0
	Yes	2/2 (100)		1/2 (50.0)	
Parosmia	No	10/12 (83.3)	1.0	6/12 (50.0)	1.0
	Yes	4/5 (80.0)		3/5 (60.0)	

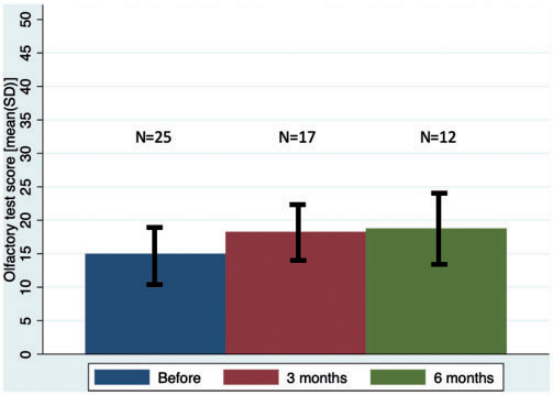

Figure 1. Comparison of the University of Pennsylvania Smell Identification Test scores administered before and 3 and 6 months after treatment ($P = .20$).

several elements. This greater diversity could theoretically reach a broader range of olfactory neurons and potentially stimulate further regeneration of the affected neuroepithelium.

We observed a considerable decrease in adherence to the OT over time. The percentage of patients adhering to OT decreased from 88% in the first 3 months to 56% at 6 months. Our lack of adherence is much higher than encountered in other studies where almost all patients concluded the training during the requested period[14,18,22,24] and similar to just 1 study in which 48% of the patients did not follow the OT as requested.[19] These values approximated the rate of adherence of medications used for other chronic diseases, which usually approaches 50%, and that can increase with care strategies in the follow-up of these patients.[33,34] The reason for discontinuation in all patients who dropped out early was the absence of noticeable improvement in the smell capacity. This cause of withdrawal is a significant challenge in the treatment of patients with olfactory disorders. Since those who withdrew did not find the treatment effective, it would appear that the percentage improving is likely an overestimate of the treatment's efficacy. Obviously, there is the need for new therapies to be developed that achieve a more rapid effect that is noticeable by the patients in order to improve treatment adherence.

Strategies described for increasing adherence to olfactory treatment include periodic telephone calls,[13] weekly or daily communications to stimulate and check the use of scented bottles,[15,24] sending e-mails,[24] short-interval visits, and changes in odor types over time.[21] Our strategy was the monthly telephone calls, which did not prevent treatment discontinuance in almost half of the patients.

No evidence was found in our limited sample, that adherence to treatment was affected by sex, age, schooling, time of olfactory loss, race, the degree of olfactory loss, etiology, education, type of training performed, phantosmia, and parosmia. Interestingly, men tended to adhere more to the training. Seven of the 8 men who started the OT continued the treatment until the sixth month. However, this trend, as well as a definitive

Table 4. Association of the Factors Studied With Efficacy in the Third and Sixth Month After the Beginning of the Olfactory Training.

Variables	Categories	Efficacy in the Third Month n (%)	*P*	Efficacy in the Sixth Month n (%)	*P*
Sex	Men	2/5 (40.0)	.54	1/5 (20.0)	1.0
	Women	2/12 (16.6)		2/7 (28.5)	
Age	<55 years	0/6 (0.0)	.24	0/3 (0.0)	.51
	≥55 years	4/11 (36.4)		3/9 (33.3)	
Race	White	2/12 (16.6)	.54	2/9 (22.2)	1.0
	Non-white	2/5 (40.0)		1/3 (33.3)	
Education	<High school	2/6 (33.3)	.38	0/3 (0.0)	.71
	High school	1/2 (50.0)		1/2 (50.0)	
	Bachelors or higher	1/9 (11.1)		2/7 (28.6)	
Degree of loss	Anosmia	4/9 (44.4)	.08	2/7 (28.6)	1.0
	Microsmia	0/8 (0.0)		1/5 (20.0)	
Etiology	Posttraumatic	1/4 (25.0)	.76	0/4 (0.0)	.55
	Postinfectious	3/9 (33.3)		2/5 (40.0)	
	Idiopathic	0/4 (0.0)		1/3 (33.3)	
Type of training	Modified	2/11 (18.2)	.58	0/7 (0.0)	.04
	Classical	2/6 (33.3)		3/5 (60.0)	
Phantosmia	No	2/8 (25.0)	.33	2/6 (33.3)	.43
	Yes	1/1 (100)		1/1 (100)	
Parosmia	No	2/6 (33.3)	1.0	2/4 (50.0)	.63
	Yes	1/4 (25.0)		1/3 (33.3)	

determination of the relative influences of the aforementioned variables, needs to be further explored in studies with larger samples.

Regarding the effectiveness of the training, 23.5% of the patients presented significant improvement after 3 months, a result that increased slightly at 6 months of treatment. These data are consistent with most of the previous studies (Table 1). Unfortunately, these values approximate or fail by a vast amount of the estimated rates of 33.3% to 67% of spontaneous recovery.[27–29,34,35] That being said, it is clear that more studies are needed to compare the efficacy rates of OT with that of controls.

We expected that the inclusion of more new odors in the OT to be more effective than the original "classic odors."[21] However, this was clearly not the case. The adherence rates in the 2 types of odor training were similar, but there was somewhat greater effectiveness in the group that employed the classical 4 odorants. One possible cause of this difference is the greater practicality of the classic treatment in relation to the modified treatment. In the latter, the patient spends more time per session due to the larger number of odorants. In addition, they had to spend the time to buy the products and change them weekly. Moreover, patients may have a stronger belief that specific odors assigned to them are more medically beneficial than grocery store odors, indirectly impacting the seriousness to which they employ the training.

Additional research on OT is still needed to clarify the time required for treatment, to verify the sustenance or reversibility of the improvement obtained by this therapy, to collect more data comparing OT with the spontaneous recovery, and to confirm if the presence of more odors in the OT kit boosts effectiveness. Furthermore, more evidence in animal models proving the effects of OT at the neuroepithelial and central nervous system level would be beneficial. Regarding future clinical research in this topic, it is worth noting that the collection of reliable data in individuals using this therapy presents several challenges, the main ones being the difficulty of long-term adherence and the large percentage of patients who do not follow the protocol as indicated.[19]

Our study has some limitations. First, the number of subjects was comparatively small. This likely precluded finding relationships between the olfactory test scores and the numerous variables that we assessed. Our power analysis suggested, however, that our sample size was sufficient to detect an effect of OT on the olfactory test measure if it was present. Second, most of our subjects were initially anosmic, as measured by the UPSIT, a condition that may have limited the efficacy of OT. It is noteworthy, however, that earlier studies based on large samples found little relationship between the magnitude of the dysfunction and changes in function over time.[29] Third, we only called the patients at monthly intervals, which may have been too infrequent to maximally encourage participation. That being said, our study does highlight the difficulty for anosmic or hyposmic patients, at least those within our Brazilian sample, to undergo long-term OT as initially described.[13] It would seem that if more initial improvement was

evident to patients, compliance would be greater. Hence, future studies are needed to further optimize the effects of odor training, if in fact they are greater than the effects of spontaneous resolution.

Conclusion

OT had an efficacy rate similar to that reported in a number of other studies that assessed spontaneous recovery. Adherence to treatment was high until the third month but declined significantly by the end of 6 months. Such decline was reportedly due to the lack of noticeable improvement in smell function.

Author Contributions

Fornazieri conceptualized and designed the study, conducted the data collection, conducted the analyses, drafted the initial manuscript, and revised the manuscript. Garcia conducted the data collection, conducted the analyses, drafted the initial manuscript, and revised the manuscript. Lopes drafted the initial manuscript and critically reviewed the manuscript. Miyazawa conducted the data collection, drafted the initial manuscript, and critically reviewed the manuscript. Silva conducted the data collection and drafted the initial manuscript. Monteiro conducted the data collection, drafted the initial manuscript, and critically reviewed the manuscript. Pinna conceptualized and designed the study and critically reviewed the manuscript. Voegels coordinated the study. Doty provided statistical guidance and critically reviewed the manuscript. All authors approved the final manuscript as submitted.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RLD is a consultant to Acorda Therapeutics, Eisai Co, Ltd, Merck Pharmaceuticals, the Michael J. Fox Foundation for Parkinson's Research, and Johnson & Johnson. He receives royalties from Cambridge University Press, Johns Hopkins University Press, and John Wiley & Sons, Inc. He is president of, and a major shareholder in, Sensonics International, a manufacturer and distributor of smell and taste tests, including the test used in this study.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Marco Aurélio Fornazieri https://orcid.org/0000-0001-5213-2337

References

1. Brämerson A, Johansson L, Ek L, Nordin S, Bende M. Prevalence of olfactory dysfunction: the Skövde population-based study. *Laryngoscope*. 2004;114:733–737.
2. Miwa T, Furukawa M, Tsukatani T, Costanzo RM, DiNardo LJ, Reiter ER. Impact of olfactory impairment on quality of life and disability. *Arch Otolaryngol Head Neck Surg*. 2001;127:497–503.
3. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg*. 1991;117:519–528.
4. Simmen D, Briner HR. Olfaction in rhinology—methods of assessing the sense of smell. *Rhinology*. 2006;44:98–101.
5. Rawson NE. Olfactory loss in aging. *Sci Aging Knowl Environ*. 2006;2006:pe6.
6. Doty RL, Kamath V. The influences of age on olfaction: a review. *Front Psychol*. 2014;5:20.
7. Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science*. 1984;226:1441–1443.
8. Schubert CR, Cruickshanks KJ, Klein BEK, Klein R, Nondahl DM. Olfactory impairment in older adults: five-year incidence and risk factors. *Laryngoscope*. 2011; 121:873–878.
9. Doty RL, Deems DA, Stellar S. Olfactory dysfunction in Parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology*. 1988;38:1237–1244.
10. Devanand DP, Michaels-Marston KS, Liu X, et al. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am J Psychiatry*. 2000;157:1399–1405.
11. Schwob JE, Youngentob SL, Ring G, Iwema CL, Mezza RC. Reinnervation of the rat olfactory bulb after methyl bromide-induced lesion: timing and extent of reinnervation. *J Comp Neurol*. 1999;412:439–457.
12. Youngentob SL, Kent PF. Enhancement of odorant-induced mucosal activity patterns in rats trained on an odorant identification task. *Brain Res*. 1995;670:82–88.
13. Hummel T, Rissom K, Reden J, Hähner A, Weidenbecher M, Hüttenbrink K-B. Effects of olfactory training in patients with olfactory loss. *Laryngoscope*. 2009;119:496–499.
14. Konstantinidis I, Tsakiropoulou E, Bekiaridou P, Kazantzidou C, Constantinidis J. Use of olfactory training in post-traumatic and postinfectious olfactory dysfunction. *Laryngoscope*. 2013;123:E85–E90.
15. Damm M, Pikart LK, Reimann H, et al. Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *Laryngoscope*. 2014; 124:826–831.
16. Haehner A, Tosch C, Wolz M, et al. Olfactory training in patients with Parkinson's disease. *PLoS One*. 2013;8: e61680.
17. Fleiner F, Lau L, Göktas Ö. Active olfactory training for the treatment of smelling disorders. *Ear Nose Throat J*. 2012;91:198–203, 215.
18. Geißler K, Reimann H, Gudziol H, Bitter T, Guntinas-Lichius O. Olfactory training for patients with olfactory loss after upper respiratory tract infections. *Eur Arch Oto-Rhino-Laryngology*. 2014;271:1557–1562.
19. Schriever VA, Lehmann S, Prange J, Hummel T. Preventing olfactory deterioration: olfactory training may

be of help in older people. *J Am Geriatr Soc*. 2014; 62:384–386.
20. Kollndorfer K, Kowalczyk K, Hoche E, et al. Recovery of olfactory function induces neuroplasticity effects in patients with smell loss. *Neural Plast*. 2014;2014:1–7.
21. Altundag A, Cayonu M, Kayabasoglu G, et al. Modified olfactory training in patients with postinfectious olfactory loss. *Laryngoscope*. 2015;125:1763–1766.
22. Konstantinidis I, Tsakiropoulou E, Constantinidis J. Long term effects of olfactory training in patients with post-infectious olfactory loss. *Rhinol J*. 2016;54:170–175.
23. Poletti SC, Michel E, Hummel T. Olfactory training using heavy and light weight molecule odors. *Perception*. 2017;46:343–351.
24. Patel ZM, Wise SK, DelGaudio JM. Randomized controlled trial demonstrating cost-effective method of olfactory training in clinical practice: essential oils at uncontrolled concentration. *Laryngoscope Investig Otolaryngol*. 2017;2:53–56.
25. Nguyen TP, Patel ZM. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss. *Int Forum Allergy Rhinol*. 2018;8:977–981.
26. Langdon C, Lehrer E, Berenguer J, et al. Olfactory training in post-traumatic smell impairment: mild improvement in threshold performances: results from a randomized controlled trial. *J Neurotrauma*. 2018;35:2641–2652.
27. Hendriks APJ. Olfactory dysfunction. *Rhinology*. 1988;26(4):229–251.
28. Duncan HJ, Seiden AM. Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. *Arch Otolaryngol Head Neck Surg*. 1995;121:1183–1187.
29. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol*. 2008;63:159–166.
30. Doty RL. *The Smell Identification Test (TM) Administration Manual*. Philadelphia, PA: Sensonics, Inc; 1995.
31. Fornazieri MA, Santos CAD, Bezerra TFP, Pinna FDR, Voegels RL, Doty RL. Development of normative data for the Brazilian adaptation of the University of Pennsylvania Smell Identification Test. *Chem Senses*. 2015;40:141–149.
32. Doty RL, Yousem DM, Pham LT, et al. Olfactory dysfunction in patients with head trauma. *Arch Neurol*. 1997;54:1131–1140.
33. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol. *JAMA*. 2006;296:2563–2571.
34. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc*. 2011;86:304–314.
35. Cavazzana A, Larsson M, Münch M, Hähner A, Hummel T. Postinfectious olfactory loss: a retrospective study on 791 patients. *Laryngoscope*. 2018;128:10–15.