Original Article

A Pilot Study of Olfactory Training in Older Hyposmic Adults

American Journal of Rhinology & Allergy
2019, Vol. 33(6) 650–656

DOI: 10.1177/1945892419858793
journals.sagepub.com/home/ajr
SAGE

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Abstract

Background: Olfactory loss is a common problem that significantly impacts quality of life. Olfactory training (OT) has been used most commonly for viral and traumatic olfactory dysfunction (OD) in younger subjects with hopes of neural regeneration, improved olfactory function, and subjective well-being. The objective of this study was to investigate the impact of a novel form of OT using 12 odors in participants over 45 years of age with objective OD.

Methods: Twenty-nine participants underwent OT using 12 standardized odor pens for a duration of 6 months. Objective OT of Threshold, Discrimination, and Identification and patient-reported outcomes were assessed at baseline and after 6 months of OT.

Results: Of the 29 participants who entered the protocol, only 16 subjects completed all 6 months of OT. Significant improvements were seen in overall Threshold Discrimination Identification (TDI; mean 4.40 points, $P = .007$), Discrimination (mean 1.44 points, $P = .019$), and Identification (mean 2.02 points, $P = .011$). Forty-four percent of subjects who completed OT achieved a mean clinically important difference of at least 5.5 points on TDI.

Conclusion: There was no significant change in patient-reported outcome measures, and no baseline factors were associated with change in olfaction. In this study, OT with 12 odors improves objective olfaction in nearly half of the older adults with OD. Further investigation is necessary to determine the impact of improved olfaction on overall health outcomes.

Keywords

olfactory dysfunction, olfactory loss, olfactory training, Sniffin' Sticks

Introduction

Olfactory loss is a common problem with significant impact upon quality of life (QOL), depression, and even mortality.[1–3] Medical and surgical treatments exist for olfactory dysfunction (OD) associated with inflammatory conditions such as chronic rhinosinusitis (CRS), and improvement in sinusitis-related OD has been shown to improve QOL.[4] The impact of nonsinusitis OD upon QOL and mortality necessitates further study of this condition. Unfortunately, few therapies exist for other etiologies of OD. Recently, olfactory training (OT) has been described for nonsinusitis OD.[5] Classic OT uses twice daily exposure to 4 odors over several months with hopes of neural regeneration, improved olfactory function, and subjective well-being. Initial reports in younger subjects with infectious, traumatic, and idiopathic OD found that 28% achieved the minimal clinically important difference (MCID) on Sniffin' Sticks over 12 weeks.[5] Other studies of OT in patients with postviral, traumatic, and aging OD report improvements between 20% and 35%.[6–8]

Modifications of OT include different training durations, the use of more odors, and the addition of topical steroids. One study compared classic OT with a 12 odor modified OT strategy in postinfectious OD over 36 weeks.[9] Clinically significant improvement in olfaction was seen in 56% of modified OT compared to 46%

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of classic OT subjects. The addition of budesonide rinses to OT in a heterogeneous group of patients improved success rates from 26.9% to 43.9%.[10] The goals of our study were to investigate the impact of a novel form of OT using 12 odors in older hyposmic subjects with OD using both objective and patient-reported outcome measures (PROMs).

Materials and Methods

Study Overview

The study was designed as a prospective nonplacebo, nonrandomized trial. The primary outcome variable was change in objective olfaction at 6 months, as measured by Sniffin' Sticks composite Threshold Discrimination Identification (TDI) score. Secondary outcome variables were olfactory-specific PROMs assessed at 6 months. We also collected objective olfactory function at 3 months as a preliminary time point. Participants were recruited from the general community in and around the Medical University of South Carolina. Subjects were eligible if they were over 45 years of age, had objective impairment of olfaction as measured by TDI score of 30 or less, and were able to complete all study questions in English. Participants were excluded if they had any active signs of acute or CRS, received oral steroids within the last month, were immunocompromised, or had a neurocognitive disorder. This protocol was approved by the Medical University of South Carolina Institutional Review Board (HR# E-607R).

Pyschophysical Olfactory Testing

Olfactory performance was assessed using Sniffin' Sticks (Burghardt Messtechnik, Wedel, Germany).[11] The subdomains of the assessment included odor threshold, odor discrimination, and odor identification. The threshold test was performed using dilutions of n-butanol in a single-staircase, 3-forced choice procedure. The discrimination test consisted of 48 pens of triplets containing 2 of the same odorant and 1 different odorant with each set presented in random order. Finally, the identification test consisted of 16 odorants that were presented at a suprathreshold intensity using multiple choice procedures. All participants were instructed to close their eyes to avoid visual identification of odorant-containing pens. Each of the 3 subdomains was scored 0 to 16. The overall results combined as a composite TDI score, with higher scores indicating better olfaction (range: 0–48).

Patient-Reported Outcomes Measures

Two olfactory-specific PROMs were utilized in this study: the modified Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS) and Impact of Olfactory Loss Visual Analog Scale (VAS). The modified QOD-NS consisted of 17 negative statements (rated scale from 0 to 3; total score ranging from 0 to 51) with lower scores indicating better QOL.[12] The VAS consisted of 9 separate items assessing the impact of OD upon mood, food enjoyment, social interactions, safety, hygiene, sex, cooking, appetite, and weight changes, rated from 0 (no impact) to 10 (biggest impact possible). Three nonolfactory-specific PROMs were used to assess impacts on depression, loneliness, and social isolation. The Patient Health Questionnaire-9 (PHQ-9) consisting of 9 questions related to depression (rated scale from 0 to 3), with a total score ranging from 0 to 30. The De Jong Gierveld Scale consists of 6 statements of emotional loneliness (rated scale from 0 to 1), with a total score ranging from 0 to 6. The UCLA Loneliness Scale consisting of 3 questions regarding social isolation (rated scale from 1 to 3, with a total score ranging from 3 to 9).

Olfactory Training

In order to control odor quality and intensity and ensure reproducibility, the OT protocol used standardized odor pens similar to those used in the Sniffin' Sticks testing (Messtechnik, Wedel, Germany). This protocol utilized 12 odors in a serial fashion, including those from the classic and modified-classic OT.[5,9] Group 1 odors consisted of rose, clove, lemon, and eucalyptus; group 2 consisted of cinnamon, peppermint, coffee, and orange; and group 3 consisted of lavender, vanilla, lilac, and ginger. Using 1 group of odors each week, the 4 odors were to be smelled in a random order with adequate sniffing of 10 seconds per each pen held approximately 1 in away from the nostrils twice daily. A new group was used each week and then repeated every 3 weeks with the goal of total duration of 6 months. A study log was given to each participant at the initial visit and 3-month follow-up to record their adherence to the training. The study log was returned to the research team at the 3-month and 6-month follow-up to calculate the participant's total compliance. Every 2 weeks, each participant was contacted via phone for a verbal update of the individual's OT progress.

Statistical Analysis

Comparison of primary (change in TDI) and secondary (change in PROMs) outcomes were done using Student's paired t test or related samples Wilcoxon signed rank test between conditions. Conditions were created based on follow-up time points (baseline vs 3 months and baseline vs 6 months), achievement of MCID of 5.5 at 6-month follow-up (nonresponders and responders),

and participants who did or did not continue OT (dropouts and completers). Comparison of independent categorical variables used the Pearson's χ^2 test or Fisher's exact test when any cells had an expected value of less than 5. Comparison of 2 independent, nonnormally distributed samples used Mann–Whitney *U* Test. Bivariate correlation analyses were completed using the Pearson correlation. For all assessments, *P* values of $\leq .05$ were considered statistically significant. SPSS 25.0 (IBM Corporation, Armonk, New York) was used for all statistical analysis.

Results

Outcomes in Overall Cohort

The initial cohort consisted of 29 participants, with 19 males and 10 females, and mean age of 66.3 years (age range: 49.3 to 93.1 years). Subjects were on average hyposmic with a mean baseline TDI of 22.7 (standard deviation, 6.7). Baseline demographics, olfactory metrics, and PROMs are listed in Table 1. Sixteen subjects completed 6 months of OT. In assessing our primary outcome variable, there were significant improvements in overall TDI, Discrimination, and Identification ($P \leq .019$ for all). TDI improved a mean of 4.40 points, D improved a mean of 1.44 points, and I improved a mean of 2.02 points. Although not significant, 3-month outcomes suggested an improvement in objective olfaction at our intermediate time point. No significant change was found in any PROMs at 6 months (Table 2).

Table 1. Baseline Demographics and Clinical Metrics.

Age, Mean (SD)	66.30 (11.93)
Sex, N (%)	
Male	10 (34.5%)
Female	19 (65.5%)
Race, N (%)	
White	21 (72.4%)
Black	7 (24.1%)
Other	1 (3.4%)
Olfactory-specific metrics, mean (SD)	
T	4.17 (2.28)
D	8.93 (2.55)
I	9.62 (3.20)
TDI	22.72 (6.77)
QOD-NS	7.54 (10.67)
Olfactory impact VAS, mean (SD)	
Mood	1.06 (2.50)
Enjoy food	2.44 (3.69)
Social interactions	0.96 (2.37)
Safety	1.71 (2.95)
Personal hygiene	1.17 (2.63)
Sex life	0.77 (2.03)
Difficulty cooking	0.96 (2.49)
Change in appetite	1.44 (2.80)
Change in weight	0.76 (1.83)
VAS total	11.27 (18.12)
Nonolfactory metrics, mean (SD)	
PHQ-9	1.83 (2.83)
DJGS	1.48 (1.55)
UCLA	3.66 (1.20)

Abbreviations: D, discrimination; DJGS, De Jong Gierveld Scale; I, identification; PHQ-9, Patient Health Questionnaire-9; QOD-NS, Questionnaire of Olfactory Disorder-Negative Statements; SD, standard deviation; T, threshold; TDI, composite "TDI" score; UCLA, UCLA Loneliness Scale; VAS, Visual Analog Scale.

Factors Associated With Change in TDI

Demographics and baseline olfactory function were analyzed in order to determine whether any factors predicted improvement in TDI with OT. Unfortunately, none of the baseline factors were associated with change in TDI, although female sex and baseline discrimination trended toward significance ($P = .069$) (Table 3). When analyzing the impact of TDI improvement upon PROMs, 14 participants had available data for all PROMs. Improvement in TDI after OT was not associated with any change in PROMs (Table 4).

Responders Versus Nonresponders

Seven of the 16 subjects (43.75%) achieved an MCID in TDI scores with 6 months of OT. We compared responders to nonresponders. While the responder group had significantly greater improvements in objective olfaction, as expected, that is, ΔThreshold ($P = .016$), ΔDiscrimination and ΔTDI ($P < .001$), there were no demographic differences between groups and there were no significant differences in changes in any PROMs over the 6-month study (Table 5).

Dropouts

Our study had 13 of the 29 subjects dropout (44.8%). We compared differences in baseline metrics between subjects who completed our study versus those who dropped out but were unable to find any differences in demographics, olfaction, or PROMs (Table 6).

Discussion

Our study of OT adds to published literature by studying a unique patient population and using validated objective and subjective metrics. Prior reports of OT contain relatively heterogeneous groups of subjects, so direct comparisons are challenging, but our results demonstrate similar olfactory outcomes. Classic OT in traumatic, infectious, or Parkinson's OD has shown

Table 2. Olfactory Outcomes.

	Baseline (n = 18)	3 Months (n = 18)	6 Months (n = 16)	Baseline Versus 3 Months	Baseline Versus 6 Months
Olfactory-specific metrics, mean (SD)				*P*	
T	3.97 (2.48)	4.79 (3.12)	4.92 (2.82)	.220	.330
D	9.00 (3.09)	9.28 (3.04)	10.44 (2.53)	.660	.019*
I	9.61 (3.60)	9.74 (3.79)	11.63 (3.24)	.290	.011*
TDI	22.58 (8.08)	23.81 (8.18)	26.98 (7.41)	.077	.007*
QOD-NS	8.41 (10.35)	–	9.80 (12.38)	–	.083
Olfactory impact VAS, mean (SD)					
Mood	1.59 (3.08)	–	1.73 (2.66)	–	.861
Enjoy food	2.76 (3.72)	–	2.15 (2.64)	–	.431
Social interactions	1.43 (2.94)	–	1.23 (2.25)	–	.638
Safety	2.44 (3.48)	–	1.65 (2.56)	–	.754
Personal hygiene	1.73 (3.23)	–	2.19 (3.30)	–	.753
Sex life	1.13 (2.53)	–	1.01 (2.31)	–	.944
Difficulty cooking	0.88 (2.24)	–	0.73 (1.37)	–	.972
Change in appetite	1.42 (2.68)	–	0.99 (1.54)	–	.600
Change in weight	1.12 (2.26)	–	1.09 (2.07)	–	.969
VAS total	14.49 (21.55)	–	12.77 (16.52)	–	.778
Nonolfactory metrics, mean (SD)					
PHQ-9	2.06 (2.82)	–	2.93 (3.65)	–	.174
DJGS	1.28 (1.74)	–	1.93 (2.31)	–	.399
UCLA	3.78 (1.44)	–	3.87 (1.96)	–	.783

Abbreviations: D, discrimination; DJGS, De Jong Gierveld Scale; I, identification; PHQ-9, Patient Health Questionnaire-9; QOD-NS, Questionnaire of Olfactory Disorder-Negative Statements; SD, standard deviation; T, threshold; TDI, composite "TDI" score; UCLA, UCLA Loneliness Scale; VAS, Visual Analog Scale.

*$P < .05$, using Students paired *t* test for D and related samples Wilcoxon signed rank test for I and TDI.

Table 3. Baseline Factors and Association With Change in TDI.

Baseline Metrics	*r*	*P*
Baseline Metrics Versus ΔTDI		
Age	−.288	.280
Sex, mean (SD)		
Male	0.70 (4.75)	.069
Female	5.41 (3.28)	
T	−.324	.221
D	−.454	.078
I	−.156	.565
TDI	−.345	.191

Abbreviations: D, discrimination; I, identification; SD, standard deviation; T, threshold; TDI, composite "TDI" score.

Table 4. Association Between Change in TDI and Change in PROMs.

	r	*P*
ΔTDI Versus ΔPROMs		
QOD-NS	−.031	.916
Olfactory impact VAS		
Mood	.259	.351
Enjoy food	.209	.454
Social interactions	.200	.475
Safety	.166	.555
Hygiene	.269	.332
Sex Life	.154	.584
Difficulty cooking	.031	.913
Change in appetite	−.114	.686
Change in weight	.114	.685
VAS total	.172	.541
Nonolfactory-specific metrics		
PHQ-9	.134	.635
DJGS	−.457	.087
UCLA	.267	.337

Abbreviations: DJGS, De Jong Gierveld Scale; PHQ-9, Patient Health Questionnaire-9; PROM, patient-reported outcome measure; QOD-NS, Questionnaire of Olfactory Disorder-Negative Statements; TDI, composite "TDI" score; UCLA, UCLA Loneliness Scale; VAS, Visual Analog Scale.

a mean TDI improvement of 3.77 (range: 0.92 to 5.0)[13] compared to our OT protocol which improved TDI a mean of 4.4. When examining likelihood of achieving an MCID in TDI scores, our success rate of 44% is comparable to previously reported success rates of 9.7% to 79% in a postinfectious series.[13]

Numerous factors are likely to play a role in success rates with OT, including age of subjects, etiology of loss,

Table 5. Responders Versus Nonresponders.

	Nonresponders (n = 9)	Responders (n = 7)	*P*
Age, mean (SD)	67.58 (13.73)	64.32 (8.06)	.837
Gender, n (%)			
Male	4 (44.4)	1 (14.3)	.308
Female	5 (55.6)	6 (85.7)	
Race, n (%)			
White	7 (77.8)	6 (85.7)	1.000
Black	2 (22.2)	1 (14.3)	
Other	–	–	
Compliance, % (SD)	72.51 (33.97)	72.98 (22.57)	.524
Olfactory-specific metrics, mean Δ (SD)			
T	−0.61 (2.26)	2.64 (2.36)	.016*
D	−0.22 (0.97)	3.71 (1.25)	<.001*
I	1.78 (2.68)	1.43 (0.98)	.758
TDI	0.94 (3.10)	7.79 (1.47)	<.001*
QOD-NS	2.13 (3.04)	2.50 (6.47)	.573
Olfactory impact VAS, mean Δ (SD)			
Mood	−0.29 (2.11)	1.72 (3.27)	.689
Enjoy food	0.02 (3.05)	1.22 (3.08)	.864
Social interactions	−0.71 (3.44)	2.03 (3.38)	.456
Safety	−1.80 (4.17)	1.70 (3.26)	.224
Personal hygiene	−0.82 (3.51)	2.45 (3.05)	.224
Sex life	−1.16 (3.14)	1.85 (3.17)	.388
Difficulty cooking	−0.98 (3.23)	0.82 (2.56)	.689
Change in appetite	−0.90 (2.70)	0.02 (2.62)	1.000
Change in weight	−0.86 (3.40)	1.13 (2.17)	.388
VAS total	−7.49 (25.57)	12.93 (21.75)	.328
Nonolfactory-specific metrics, mean Δ (SD)			
PHQ-9	1.00 (2.87)	0.83 (1.83)	.864
DJGS	0.56 (1.42)	0.00 (1.41)	.529
UCLA	−0.22 (0.83)	0.17 (0.98)	.689

Abbreviations: D, discrimination; DJGS, De Jong Gierveld Scale; I, identification; PHQ-9, Patient Health Questionnaire-9; QOD-NS, Questionnaire of Olfactory Disorder-Negative Statements; SD, standard deviation; T, threshold; TDI, composite "TDI" score; UCLA, UCLA Loneliness Scale; VAS, Visual Analog Scale.
*$P < .05$, using related samples Wilcoxon signed rank test.

Table 6. Comparison of Dropouts to Subjects Who Completed 6 Months of Therapy.

	Dropouts (n = 13)	Completers (n = 16)	*P*
Age, mean (SD)	66.48 (13.07)	66.15 (11.37)	.914
Gender, n (%)			
Male	5 (38.5%)	5 (31.3%)	.714
Female	8 (61.5%)	11 (68.8%)	
Race, n (%)			
White	8 (61.5%)	13 (81.3%)	.297
Black	4 (30.8%)	3 (18.8%)	
Other	1 (7.7%)	0 (0.0%)	
Baseline olfactory metrics, mean (SD)			
T	4.25 (2.05)	4.11 (2.51)	.812
D	8.92 (2.25)	8.94 (2.84)	.812
I	9.15 (2.76)	10.00 (3.56)	.329
TDI	22.33 (5.69)	23.05 (7.71)	.398
QOD	5.69 (10.63)	9.13 (10.81)	.586
Olfactory impact VAS, mean (SD)			
Mood	0.19 (0.20)	1.77 (3.24)	.249
Enjoy food	2.78 (4.09)	2.17 (3.44)	.846
Social interactions	0.78 (2.30)	1.11 (2.50)	.650
Safety	0.68 (1.94)	2.54 (3.40)	.121
Personal hygiene	0.65 (1.63)	1.59 (3.22)	.398
Sex life	0.59 (1.67)	0.91 (2.33)	.746
Difficulty cooking	0.98 (2.73)	0.93 (2.36)	.812
Change in appetite	0.93 (2.73)	1.85 (2.87)	.288
Change in weight	0.15 (0.18)	1.26 (2.37)	.110
VAS total	7.74 (12.26)	14.13 (21.75)	.351
Baseline nonolfactory metrics, mean (SD)			
PHQ-9	1.08 (2.75)	2.44 (2.83)	.062
DJGS	1.38 (1.33)	1.56 (1.75)	.983
UCLA	3.38 (0.65)	3.88 (1.50)	.746

Abbreviations: D, discrimination; DJGS, De Jong Gierveld Scale; I, identification; PHQ-9, Patient Health Questionnaire-9; QOD, Questionnaire of Olfactory Disorder; SD, standard deviation; T, threshold; TDI, composite "TDI" score; UCLA, UCLA Loneliness Scale; VAS, Visual Analog Scale.

variable improvement in specific aspects of olfaction, number of odors used, duration of therapy, and compliance. Our study population was selected from middle age to elderly volunteers who were not seeking medical attention but had documented hyposmia. This is in contrast to most subjects with traumatic or postviral OD who are younger, more aware of and impacted by their acute loss, and likely more motivated to comply with OT. When examining OT studies in older subjects, there are 2 prior reports. The first study examined adults with a mean age of 81 years who used classic OT for 3 months. While OT did not improve olfactory function, it may have prevented natural decline when compared to a control group.[14] Our study very well may have had greater success due to longer duration of OT (3 months vs 6 months) in a younger population (mean of 66.3 years vs 81 years). The second study examined normosmic adults with mean age of 60 years and used classic OT for 5 months. Response rate for improving by an MCID was 20%.[8] While our mean age was similar to this study, we only included subjects who were hyposmic at baseline. Thus, our subjects had greater room for improvement with OT, which likely contributed to our higher success rate.

Our study found that TDI improvements in the overall cohort were driven by improvements in D and I with no significant change in T. However, when examining responders, they appeared to have improvements in T and D. Meta-analysis of other OT studies found that T did not improve, but D and I did.[13] It is possible that central changes after OT result in neural regeneration or neural plasticity, thus improving discrimination and identification.

When examining the number of odors and duration of OT, modified OT using 12 odors in subjects with postinfectious OD has reported 44% success rate in comparison to classic OT used in the same study. Given the significant heterogeneity in study designs, it is difficult to determine the optimal number of odors, but increasing the number may be beneficial. Duration of OT appears to be relatively important. In our study, olfaction improved at 3 months but not significantly and others have shown similar continued improvement between 3 and 6 months.[9]

OD is known to have significant impacts upon QOL; however, this is likely to be more significant in subjects with acute olfactory loss such as traumatic and postviral OD. Older adults who have slow progression of OD appear to be less impacted. Prior reports of normosmic CRS patients have shown QOD-NS scores of 9.9.[15] This compares to a mean QOD-NS of 7.54 in our initial cohort and baseline QOD-NS of 8.4 in subjects who completed OT. Thus, while our baseline population was hyposmic, their olfactory and nonolfactory PROMs indicate that they were essentially asymptomatic. Given this lack of baseline impact upon QOL, it is not surprising that OT was not associated with any changes in PROMs. The association of OD in the elderly with mortality led us to examine associations with depression or social isolation; however, we did not find any. It remains to be determined whether OT that reverses OD may have a subsequent impact upon mortality.

Compliance is obviously critical for any therapy to be successful. Subjects who completed OT in our study reported compliance rates of 73% which is similar to other reports.[16] Unfortunately, in our study, compliance rates were not associated with clinical response. Given the need for compliance over a 6-month period, it would be ideal to identify subjects likely to improve with OT. Unfortunately, in our study, we were unable to identify any factors associated with changes in TDI; however, 1 study reported baseline TDI scores and the participant's age as significant predictors of changes in TDI ($P < .001$).[16]

Our study has several limitations, including lack of placebo group, relatively small sample sizes, and high dropout rate of 45%, compared to published dropout rates of 25%.[8] Such high dropouts are likely due to the time intensive nature of OT, the lack of awareness of baseline OD, and lack of impact of OD upon their current QOL. Dropout rates could be improved in the future studies by compensating subjects or if OT is found to positively impact other aspects of health. Strengths of our study include its prospective nature, limitation to idiopathic hyposmic subjects, use of standardized OT pens, and validated PROMs.

Conclusion

OT with 12 odors was found to improve objective olfaction in nearly half of the older hyposmic adults. Further investigation is warranted to determine whether prevention of olfactory loss by OT impacts mortality and other comorbidities. Similar to treatments for other asymptomatic conditions, such as hypertension or high cholesterol, willingness to complete OT could improve whether participants become aware of direct links to future health.

Acknowledgments

The authors thank Tegan Noonan for her help with support and recruitment of participants.

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: Z. M. S. is a consultant for Optinose, Olympus and Healthy Humming, LLC and on the advisory board for Regeneron and Novartis. R. J. S. is a consultant for Olympus, Sanofi, Optinose, Healthy Humming, LLC, and Arrinex. None are affiliated with this study. There are no disclosures for J. M. L.

Funding

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

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