Flavor Enhancement in Daily Life of Patients with Olfactory Dysfunction

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Abstract

Introduction Patients with olfactory dysfunction report deterioration of taste due to loss of flavor, leading to less food enjoyment, alterations in dietary behaviors and stress. The aim of this study was to introduce flavor enhancement to investigate its acceptance and possible effects on quality of life.

Methods In this prospective, controlled, randomized, single-blinded, cross-over pilot study, we recruited 30 olfactory dysfunction patients, of which 16 were hyposmic and 14 anosmic. After single-blinded triangle flavor discrimination test, flavor drops were randomized either in high or low concentration for 14 days and vice versa for another 14 days. Records included a daily diary and the questionnaire of olfactory disorders.

Results Usage rates were excellent with 82.2% of all days, while drops were mainly used for breakfast (44.6%, $p < 0.05$). Hyposmics used flavor enhancement on significantly more days (median = 14) compared to anosmics (median = 11, $p = 0.0094$). QOD improved in 12 patients to a meaningful extent.

Conclusions In this pilot study, we show that flavor enhancement is feasible accompanied by high compliance and acceptance in olfactory dysfunction patients. Flavor drops were used regardless of low or high concentrations with no adverse events noted.

Implications

Our findings give rise to further studies illuminating the possible advantages of flavor enhancement in patients with olfactory disorders.

Keywords Olfactory disorders · Olfactory test · Quality of life · Chronic disease

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Introduction

Multisensory flavor perception is based on the combination of smell, taste, and trigeminal activation (including perception of temperature and texture) (Bojanowski and Hummel 2012). Odorant molecules can be perceived either orthonasally via sniffing or retronasally through the pharynx. Retronasal olfaction constitutes the main part of flavor perception (Shepherd 2006). Patients with olfactory dysfunction frequently report deterioration of taste due to loss of flavor, leading to less food enjoyment, alterations of dietary behaviors (Aschenbrenner et al. 2008), emotional stress (Stevenson 2009), and lower quality of life (Miwa et al. 2001). A recent study postulated retronasal perception to be a better predictive factor for quality of life than orthonasal (Oleszkiewicz et al. 2019a). This aligns with the mentioned concept of retronasal olfaction contributing to flavor perception and hence food enjoyment. The vast majority of patients with olfactory dysfunction report decreased flavor perceptive capacity (i.e., “food tastes dull”), and some state their flavor perception to be normal may be tested abnormal (Liu et al. 2019). This highlights that the flavor system needs attention in olfactory dysfunction patient counseling and treatment. Multiple drug treatment approaches have been attempted so far. Researchers assessed intranasal administration of corticosteroids (Heilmann et al. 2004), sodium citrate (Reden et al. 2011; Whitcroft et al. 2016a, b), insulin (Schopf et al. 2015), or theophylline (Henkin et al. 2012), as well as systemic treatment with corticosteroids (Heilmann et al. 2004; Seo et al. 2009; Jiang et al. 2010, 2015; Schriever et al. 2012; Tian et al. 2015), zinc (Lyckholm et al. 2012; Jiang et al. 2015), rasagiline (Haehner et al. 2013, 2015), vitamin A (Reden et al. 2012), theophylline (Henkin et al. 2009), ginkgo biloba (Seo et al. 2009), vitamin B (Heilmann et al. 2004), caroverine (Quint et al. 2002), pentoxifylline (Gudziol and Hummel 2009), or alpha-lipoic-acid (Hummel et al. 2002). None of these showed sufficient evidence of efficacy and should not be recommended following the position paper on olfactory dysfunction (Hummel et al. 2017). Systemic or intranasal corticosteroids are only recommended in dysosmic patients with chronic rhinosinusitis and other inflammatory diseases of the nasal mucosa (Hummel et al. 2017). Beside these drug treatment attempts, orthonasal smell training has been established as a first line option for dysosmic patients (Hummel et al. 2017). Retronasal training (i.e., flavor training) has only been investigated in a pilot study so far and further data is needed (Besser et al.).

Despite increasing recognition for orthonasal olfactory training, less is known about retronasal stimulation (i.e., flavor training) as a therapy option (Besser et al. 2020).

In general, olfactory training is recommended meal-independent (i.e., training sessions are separated from meals) with the goal to boost neuronal recovery (i.e., as a therapeutic strategy). However, the recovery process may take years, and hence, there is an evident need to investigate for strategies to make dishes more appealing for this patient group (i.e., coping strategies or strategies to improve quality of life). Schiffman and Warwick proposed flavor enhancement of foods to be beneficial for elderly retirement-home residents leading to an increased food intake (Schiffman and Warwick 1993), while others postulated no distinct effect (Forde et al. 2002). Since sensory perception and pleasantness of food flavors decrease with age (de Graaf et al. 1994), other studies followed comparing younger probands with the elderly. While elderly probands had increasing food consumption of flavor amplified yoghurt, consumption levels decreased in young participants showing an opposite effect (Griep et al. 1997). Another study showed that increased food enjoyment led to increased food intake, positive effects on the immune system, and improvement of grip strength (Schiffmann and Warwick 1993). However, addition of flavor and/or monosodium glutamate also showed no increase in energy intake nor in body weight gain in the elderly (Essed et al. 2007), thus leaving flavor amplification still as controversially discussed. The aim of the present study was to introduce flavor enhancement as a new supportive care option in a group of patients with olfactory dysfunction, investigate its acceptance, and look for possible effects on olfactory-specific quality of life.

Patients and Methods

Study Type and Recruitment

This prospective, controlled randomized, single-blinded, cross-over study was performed at the Department of Otorhinolaryngology, Head and Neck Surgery of the Medical University of Vienna and conducted according to the declaration of Helsinki and approved by the local ethics committee (Approval No. EK-Nr.: 2242/2018). All data were collected between April and November 2019. Informed consent was obtained prior to inclusion. All patients were referred to the clinic by otolaryngologists due to chemosensory complaints. After they underwent structured medical history including detailed ear-nose-throat-examination, patients were classified according to underlying causes (reason) for olfactory dysfunction (Hummel et al. 2017). Radiologic imaging was performed whenever clinically applicable. Only patients between the age of 18 and 85 years with quantitative olfactory dysfunction were included. Olfactory dysfunction was assessed using validated testing methods (see

below). Exclusion criteria were impaired cognitive function, malignancies of the head and neck region and/or previous head and neck radiation therapy, abuse of smoking tobacco, alcohol or addictive drugs, fructose intolerance, and/or an increased likelihood of aspiration. Overall, each patient visited 3 times. At the first visit, we evaluated eligibility criteria including chemosensory testing and a triangle test (see below).

Single-Blinded Triangle Flavor Discrimination Test

For this triangle test and for flavor enhancement (see below), flavor drops, containing water, flavor (vanilla, coconut or strawberry), and sweetener sucralose, were used (commercially available, Gymqueen®). Other taste stimuli than sweet (such as monosodium glutamate or salt) were not used. As in the nature of a pilot study (complied with the Consort Statement; checklists and flow diagram can be found in supplementary data), the ability to discriminate flavor drops in foods in olfactory dysfunction patients (especially in anosmic patients) was unknown a priori and therefore pre-evaluated with a triangle test before starting flavor enhancement. For each test, 5 flavor drops were mixed with one 250 ml plain yoghurt cup. Two other plain yoghurts remained unflavored. The blindfolded patient was offered spoons with yoghurt and had to discriminate the flavored one. In between tests, patients rinsed their mouths with water. Study eligibility depended on positive completion of this triangle flavor discrimination test two times out of three tries. Accordingly, one patient was excluded at first visit, because he was unable to discriminate flavored from unflavored yoghurt. Furthermore, intensity and hedonic ratings, which has been assessed after each test run, as well as possible individual usefulness of added flavor at the end of the test, were documented using visual analog scales ranging from

1 to 10 for intensity (1 = poorly intensive to 10 = extremely intensive) and – 4 to + 4 for hedonics (– 4 = very unpleasant to + 4 = very pleasant).

Flavor Enhancement

For flavor enhancement, patients were randomized in 2 groups (by a preprogrammed randomization list). According to grouping, patients were supplied with flavor drops (Gymqueen®) either in high (= verum) or low (= pseudo-placebo) concentration. To lower concentration in case of pseudo-placebo, 3 drops were diluted in 15 ml water. The flavor was still identified by normal controls, but not by olfactory dysfunction patients. Investigators in direct patient contact were blinded to this process (i.e., were not aware which patients received high or low concentrations first; group A = first verum then pseudo-placebo; group B vice versa). Patients were instructed to use 5 to 10 drops at least once a day for the study time period to enhance their meals. Concentrations interchanged at visit 2 (V2) after 2 weeks (i.e., group cross-over) and flavor enhancement was continued until the end of study after 4 weeks (for study profile see Fig. 1). Usage of flavor drops (number of drops and type of flavor) was recorded 3 times a day in form of a paper–pencil diary.

Chemosensory Testing

Orthonasal Olfactory Function

Orthonasal olfaction was assessed using the Sniffin' Sticks test battery (Burghart Medical Technology, Wedel, Germany), testing for the composite score of odor threshold [*T*], odor discrimination [*D*], and odor identification [*I*] (i.e., TDI score). Detailed description of

Fig. 1 Flavor drops were issued single-blinded either in high (verum) or low concentration (pseudo-placebo) in a cross-over design. At visit 1 (= V1) patients received batch A of either “verum” or “pseudo-placebo” together with diary #1, while at visit 2 (= V2) after 2 weeks, patients returned batch A and returned diary #1, they received batch B of either “verum” or “pseudo-placebo” vice versa and diary #2. At the end of study (= EOS), batch B and diary #2 were returned.

Sniffin' Sticks test (threshold, discrimination, identification), Candy Smell Test, and Taste Strip Test were performed at V1; The Questionnaire of Olfactory Disorders and Patient Health Questionnaire-2 were performed at all three visits; 4-item FlavorEnhancement-Questionnaire (4-IQ) was assessed at EOS. Graphics used: icons generated from www.flaticon.com

administration can be found elsewhere and normative data sets are available for comparison (Kobal et al. 2000; Liu et al. 2019; Erskine and Philpott 2020). For the purpose of this study, TDI-scores higher than 31 were defined as normosmia and TDI-scores less than 31 and higher than 16 as hyposmia. Functional anosmia was defined as TDI scores equal or less than 16 (Oleszkiewicz et al. 2019b). Assuming normosmia, subjects with scores higher than 31 were excluded from this investigation ($n = 3$).

Retronasal Olfactory Function

Retronasal olfaction was tested using the Candy Smell Test (Renner et al. 2009; Haxel et al. 2011). Validated in a 23-item version, this investigation assessed flavor identification skills using a 27-item version (for aromas and distractors please see (Essed et al. 2007)). These candies contain 500 mg sorbitol and one target aroma (i.e., flavor), which has to be identified in a forced-choice manner among 4 possible answers. The Candy Smell Test score is the summed score of correct answers (hence, a maximum of 27 points can be reached).

Gustatory Function

Gustatory function (i.e., taste) was tested using the clinically validated Taste Strip Test (Mueller et al. 2003) for the 4 basic qualities (sweet, sour, salty, bitter) in a non-forced-choice manner. Methodology is described elsewhere (Mueller et al. 2003, 2008; Welge-Lüssen et al. 2010) and Taste Strip Test-scores lower than 9 were defined as hypogeusia (Kobal et al. 2000; Mueller et al. 2003).

Questionnaires

Questionnaire of Olfactory Disorders (QOD)

The German version of the QOD (Frasnelli and Hummel 2005) was used to evaluate baseline olfactory-specific quality of life in enrolled patients and detect possible changes in quality of life in the course of this trial. We applied the 19-item QOD (Shu et al. 2011) version dividable into two subdomains: 17 negative statements (QOD-NS) with higher scores indicating a higher degree of psychological strain and 2 positive statements (QOD-PS) reflecting the coping abilities (higher scores representing better adjustment of patients to their olfactory dysfunction). Changes in QOD-NS scores were interpreted as meaningful when reaching a difference of ≥ 6 points according to Mattos et al. (Mattos et al. 2018).

Patient Health Questionnaire-2 (PHQ-2)

To assess depression severity, often associated with olfactory disorders (Croy et al. 2014), a German version of the PHQ-2 was used for a quick assessment in this clinical setting. Two questions on depression symptoms are rated on a 4-point scale (0 = not at all; 1 = several days; 2 = more than half of the day; 3 = this is the case every day). Summed scores of 3 and higher indicate depression (Kroenke et al. 2003).

4-Item Flavor Enhancement-Questionnaire (4-IQ)

For the purpose of this study, 4 additional questions (Table 1) were defined in order to assess patients' experience with flavor drops.

Table 1 4-Item Flavor Enhancement-Questionnaire (4-IQ); results with numerous scale reaching from 1 (not at all) to 10 (definitely). Results for all patients included, as well as hyposmics and anosmics. Each question result separately and overall mean with standard deviation (= SD)

4-IQ	Question text	Answers ranked from 1 = not at all; to 10 = definitely	Results					
			All	Mean	Hyposmics	Mean	Anosmics	Mean
#1	FE improves my flavor perception of meals	1—2—3—4—5—6—7—8—9—10	2.7 (2.3 SD)	10.2 (7.6 SD)	2.0 (1.7 SD)	7.5 (4.8 SD)	3.3 (2.6 SD)	12.6 (9.0 SD)
#2	FE makes me enjoy my meals more	1—2—3—4—5—6—7—8—9—10	2.3 (2.2 SD)		1.6 (1.0 SD)		3.0 (2.7 SD)	
#3	I would use FE henceforth after finishing this study	1—2—3—4—5—6—7—8—9—10	2.2 (2.0 SD)		1.6 (1.3 SD)		2.8 (2.3 SD)	
#4	I would recommend FE after finishing this study	1—2—3—4—5—6—7—8—9—10	2.9 (2.4 SD)		2.3 (1.7 SD)		3.4 (2.8 SD)	

Statistical Analysis

GraphPad Prism 8.4.5 (GraphPad Software, Inc., La Jolla, San Diego, CA, USA) was used for statistical analysis and graphical visualization. Normality of data was assessed based on histograms. Data are presented as mean and SD, as indicated. Differences in flavor drop usage (absolute numbers) between morning, noon, and evening dishes were assessed using repeated-measures one-way ANOVA (rm-ANOVA) and Tukey's multiple comparisons test for the hyposmic and anosmic patient group. Group differences were tested using the unpaired sample *t* test or the Mann–Whitney *U* test, depending on the distribution. Correlation analyses were performed using the Pearson correlation coefficient (*r*). A *p* value of <0.05 was required for statistical significance.

Results

Subjects and Baseline Results

In this study, we included 30 patients (9 males, 21 females, mean age 55.3 ± 18.4 , range 21–83 years) (Table 2). Underlying causes were idiopathic ($n = 13$) and postinfectious ($n = 11$), followed by sinonasal ($n = 3$) and posttraumatic ($n = 3$).

Chemosensory testing revealed mean/standard deviation (SD) test scores of 17.3/6.4 (TDI), 10.5/3.9 (Candy Smell Test), 9.7/3.3 (Taste Strip Test), categorizing approximately half of patients hyposmic ($n = 16$) and half anosmic ($n = 14$). Less than one-third of patients included were identified with

dysgeusia ($n = 8$). Ortho- and retronasal olfactory test score correlated significantly ($r_{30} = 0.7473$; $p < 0.0001$). Triangle test of discrimination of flavor drops showed high values for intensity (7.8/10, 2.4 SD) and suggestively low rates for hedonic ratings (+1.3, 2.1 SD; range −4 to +4). All patients included could discriminate the flavored yoghurt three out of three times. Screening for depression was negative in the majority of patients with olfactory dysfunction and revealed PHQ-2 mean scores of 1.3 (1.8 SD) at V1, with 5 patients showing scores above 3, related to depression. Mean QOD-NS scores were 18.5 ± 9.2 and 2.2 ± 1.9 for the QOD-PS, both not correlating significantly with olfactory test results (all $p > 0.780$).

Acceptance and Participation Compliance

When asked after passing the triangle test, the majority of patients expected a potential advantage from the flavor drops on their everyday life (5.4/10, 2.2 SD). Analyzing the diary, patients showed excellent acceptance and usage rates of flavor drops, regardless of higher (verum) or lower (pseudo-placebo) concentration, with 82.2% of all days (11.5/14, 3.0 SD; Table 3).

Patients utilized flavor enhancement mainly for breakfast (44.6%), followed by dinner (30.6%) and lunch (24.8%), measured by the number of used flavor drops. One-way rm-ANOVA revealed a significant effect of daytime (morning, noon, and evening) on the use of flavor drops (absolute number of drops): hyposmics [$F(1.689, 45.59) = 5.252$, $p = 0.012$] and anosmics [$F(1.501, 46.53) = 4.976$, $p = 0.0181$] (Fig. 2).

Table 2 Demographic, causal data and chemosensory scores

Gender	f 21	m 9						
Cause of OD	T ($n = 3$)	V ($n = 11$)	I ($n = 13$)	S ($n = 3$)				
	Mean	SD	Range					
Age	55.3	18.4	(21–83)					
BMI	26.0	4.8	(18.9–42.1)					
Duration of OD (in months)	28.9	44.4	(1–204)					
TT intensity	7.8	2.4						
TT hedonics	+1.3	2.1						
TT advantage	5.4	2.2						
	All ($n = 30$)		Hyposmia ($n = 14$)		Anosmia ($n = 16$)		Dysgeusia ($n = 8$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
TDI	17.3	6.4	22.7	4.6	12.5	2.9	15.9	5.5
CST	10.5	3.9	13.0	3.9	8.3	2.5	11.3	2.8
TST	9.7	3.3	10.1	2.8	9.4	3.7	5.0	1.6

BMI body mass index, *CST* Candy Smell Test, *f* female, *I* idiopathic, *m* male, *OD* olfactory dysfunction, *S* sinonasal, *SD* standard deviation, *T* posttraumatic, *TDI* threshold, discrimination, identification, *TST* Taste Strip Test, *TT* triangle test, *V* postinfectious

Table 3 Compliance and days of usage/non-usage per patient (maximum = 14 days)

			Days of usage	Days of non-usage	Daytime usage		
					Breakfast	Lunch	Dinner
All	Mean		11.5	2.5			
	SD		3.0	3.0			
	In %		82.2	17.8	44.6	24.8	30.6
Verum	Mean		11.6	2.4			
	SD		3.2	3.2			
	In %		83.1	16.9	42.6	26.5	30.9
Pseudo-placebo	Mean		11.2	2.8			
	SD		2.9	2.9			
	In %		80.0	20.0	46.3	23.3	30.4
Anosmia	Mean		10.5	3.5			
	SD		3.2	3.2			
	In %		75	25	44.1	27.0	28.9
Hyposmia	Mean		12.4	1.6			
	SD		2.4	2.4			
	In %		88.6	11.4	45.2	22.3	32.6

SD standard deviation

Fig. 2 Quantification (mean $\pm$ SD) of the number of flavor drops used during breakfast, lunch, and dinner in the (A) hyposmic and (B) anosmic groups. Groups were compared by the rm-ANOVA test with post-hoc Tukey's test. * $p < 0.05$

Tukey's post hoc test for the hyposmic group revealed that significantly more flavor drops were used for breakfast compared to lunch ($p = 0.0019$). No significant difference in flavor drop usage was found between breakfast and dinner ($p = 0.3102$), nor between dinner and lunch ($p = 0.2779$). Similarly, Tukey's post hoc test for the anosmic group revealed that significantly more flavor drops were used for breakfast compared to lunch ($p = 0.0108$). No significant difference in the use of

flavor drops was found between breakfast and dinner ($p = 0.1169$), nor between dinner and lunch ($p = 0.9094$). Furthermore, no adverse events were reported by all patients involved (e.g., nausea, vomiting, low appetite). Usage rates were approximately the same for verum (83.1%) and pseudo-placebo (80.0%) (Table 3) showing slightly higher drops used in total for low-intensity drops (163.2; 46.1 SD) compared to high-intensity drops (134.5; 44.4 SD).

Table 4 Questionnaire results for subgroups

		All				Anosmia				Hyposmia			
		V		PP		V		PP		V		PP	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
QOD-NS	Base	17.1	9.8	16.5	9.5	18.6	10.9	18.4	9.4	16.3	9.5	14.7	5.2
	Change	1.6	1.6	1.3	2.1	0.2	2.5	1.7	3.1	3.3	2.7	0.8	1.4
PHQ-2	Base	1.6	2.0	1.0	1.6	1.3	2.0	0.6	0.8	2.0	2.1	0.9	1.5
	Change	0.3	1.3	1.0	1.4	0.8	1.3	0.2	1.0	0.5	0.9	0.9	1.4

Mean changes were evaluated for either verum (= V) or pseudo-placebo (= PP) group

According to the cross-over design, baseline values were either taken at V1 or V2 and correlated with either V2 or EOS. *Base* baseline values, *PHQ-2* patient health questionnaire-2, *QOD-NS* questionnaire of olfactory disorders, negative statements, *SD* standard deviation

Fig. 3 Days of flavor enhancement use in hyposmic and anosmic patients. * $p < 0.05$

Quality of Life Outcome

Evaluation of olfactory-specific quality of life showed mean scores for QOD-NS of 18.4 (10.9 SD) for verum and 18.5 (10.9 SD) for pseudo-placebo at V1 (Table 4).

Analyzing the QOD-NS individually, 12 patients showed significant minimal clinical importance difference (MCID) of 6 and higher, of which 7 were correlating with verum, while 5 patients had relevant after using pseudo-placebo at follow

up visit. 4-IQ showed mean results of 10.2 (7.6 SD) for the study population, respectively (detailed results are shown in Table 1).

Anosmics versus Hyposmics

Interestingly, hyposmics used flavor enhancement on significantly more days (median = 14) compared to anosmics (median = 11, $U = 280$, $p = 0.0094$) (Fig. 3). Individual changes in QOD-NS and PHQ-2 are outlined in Table 4. The anosmic group showed no significantly higher mean QOD-NS at baseline (V1; 20.0, 9.5 SD) compared to the hyposmic group (17.5, 9.5 SD), [$t(28) = 0.6121$, $p = 0.545$]. Regarding the 4-IQ, anosmic patients showed mean values of 12.6 (9.0 SD), while hyposmics had scores of 7.5 (4.8 SD).

Discussion

Major Results

In this study, we demonstrate that flavor enhancement is feasible and well accepted among patients with olfactory dysfunction, regardless of randomly assigned high or low concentrations. Even though orthonasal smell training showed promising results and is recommended in patients with several etiologies (Hummel et al. 2017), additional options are dearly needed to ease the great psychological burden of our patients suffering from this condition. Considering limited data on retronasal stimulation and its potential benefit (flavor training, Besser et al. 2020), it was evident to pursue this possible new supportive care option. Previous studies on flavor enhancement mainly focused on elderly people (with assumed presbyosmia) (Schiffman et al. 1993; Schiffman 2000; Mathey et al. 2001; Koskinen et al. 2003; Essed et al. 2007; Schiffman et al. 2007). Promising findings showed increased food intake (Schiffman and Warwick 1993; Mathey et al. 2001), better immune function (Schiffman and Warwick 1993; Schiffman 2000),

and higher food acceptance (Schiffman 2000). However, no increase in dietary intake (Koskinen et al. 2003; Essed et al. 2007) nor food acceptance (Koskinen et al. 2003) was reported, mirroring a still controversially discussed benefit of flavor enhancement.

In this study's planning phase, it was not clear whether patients were going to be able to detect flavor enhancement in meals and hence would comply with the study protocol. For this reason, we applied a single-blinded triangle test before inclusion. Flavor enhancement was well discriminated probably due to its sweet character. Participants stated moderately high expectations in individual benefit of flavor enhancement, as measured by visual analog scales. Since flavor drops contained sucralose without calories, no restrictions in recruitment related to BMI or diabetes had to be implemented.

Patients showed unexpected high acceptance rates as displayed in the diaries: flavor enhancement was used for approximately 10 days, mainly for breakfast. Patients evidently took advantage of the sweet character when consuming dishes that were sweet (e.g., cereals in the morning). Even in cases of doubt toward the product (as reflected in questionnaires at V2), either regarding the non-detectable pseudo-placebo drops or the prominent sweet component, patients continued using flavor enhancement. This might be due to patients' hopes of benefits for olfactory function. On the one hand, patients were looking for short-term improvement of flavor perception and taste experience. An additional reason for continuous use during the study period despite low benefit might be the fact that patients were highly motivated due to high psychological strain. This shows the need of patients for improved management of smell disorders in terms of coping strategies.

The MCID score for the QOD-NS was used for interpretation of meaningfulness in changes (Mattos et al. 2018). Mean changes in QOD-NS did not show significant results in favor of verum concentrations. However, twelve patients showed meaningful decreases in QOD-NS scores, of which 7 were in verum and 5 in pseudo-placebo patients. Comparing hyposmic with anosmic patients, we found no major differences for verum or pseudo-placebo. Altered concentrations therefore did not seem to bother nor help patients. This means that patients might have not noticed a difference between verum and pseudo-placebo, or that the intensity of flavor was too low compared to the prominent taste of the artificial sweetener used in the flavor drops. Another possibility might be the presence of a yet unknown flavor threshold regardless of its intensity, which could not be identified in this pilot study. Interestingly, hyposmics used the flavor drops significantly longer than anosmics. Hyposmics have better olfactory function and therefore better flavor perception. This might have led to prolonged usage.

The screening for depression (for instance using the established PHQ-2) is useful, because negative mood attributes represent a greater burden to patients (Kroenke et al. 2003). PHQ-2 evaluation showed no major depression in the study group, classifying this group of olfactory dysfunction patients as mentally stable. Interestingly, the burden of olfactory loss in this study cohort was displayed by comparably low QOD-NS scores to previous studies (Shu et al. 2011; Green et al. 2012), but still high interest of patients in additional treatment options.

Limitations

Since this was a pilot study, the study population was fairly small ($n=30$). In order not to risk dropouts, total investigation time period was held low at 4 weeks, thus resulting in excellent patients' acceptance and intention to finish the study. To compensate for the small study population, a cross-over-design was chosen, however with the limiting factor of a short observation period. Long-term effects and delayed improvement could not be investigated for. Previous studies on flavor enhancement included mostly flavors, but also monosodium glutamate—hence a basic taste quality (Schiffman 2000; Mathey et al. 2001; Essed et al. 2007). Furthermore, it has been postulated that enhancing retro-nasal odors by sweetener intensified the flavors cherry and vanilla (Green et al. 2012), guiding us to use sweet flavors in this study. In food science, researchers already focused on aroma enhancement strategies (Hopfer et al. 2015; Brown et al. 2020), which may help in future studies on quality of life and olfactory dysfunction. Despite these promising expectations, some patients in our study population found the artificial sweetener disturbing and unpleasant.

Nevertheless, usage rates were 80% of the time or more, showing very high compliance even when considered uncomfortable. This might be due to psychological effects (Kadi et al. 2012). Olfactory dysfunction patients usually experience less empathy in health care workers for their disease (Erskine and Philpott 2020) and participation in studies on olfactory dysfunction in general may help in increasing attention for this disease. Another key aspect is that therapeutic options of olfactory dysfunction patients are often at an end, thus enhancing the willingness for patients to try new methods and therapies (Besser et al. 2019).

Conclusions

In this pilot study, we show that flavor enhancement is feasible accompanied by a high compliance and acceptance rate in patients with olfactory dysfunction. It was well

tolerated with no adverse events noted. Flavor enhancement was used regardless of low or high concentrations.

Implications

Since acceptance and compliance were high, flavor enhancement bears a high potential to become an additional treatment option in olfactory dysfunction patients. Variability of usage of flavor enhancement was limited due to sweet components. Therefore, in future studies, multiple different flavors could be offered, leading to a higher spectrum of dishes appropriate for flavor enhancement. Furthermore, larger study groups are needed for higher statistical power, as well as a longer time period and follow-up for long-term effects and possible delayed improvement. Since normative data for PHQ-2 and IQ-4 are missing, greater study sets are needed to illuminate the benefit of flavor enhancement.

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Declarations

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. It was approved by the Medical University of Vienna Ethics Committee (Approval No. EK-Nr.: 2242/2018).

Informed Consent Informed consent was obtained from all individual participants included in the study, where they all gave their written consent and were remunerated for their participation.

Conflict of Interest The authors declare no conflict of interest.

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