Olfactory Implant: Demand for a Future Treatment Option in Patients With Olfactory Dysfunction

Gerold Besser, MD; David T. Liu, MD; Bertold Renner, MD; Thomas Hummel, MD; Christian A. Mueller, MD

**Objectives:** Therapeutic options in olfactory dysfunction (OD) are limited. Numerous studies have shown impact of OD on quality of life. Lately, various studies support benefits of olfactory training, but therapy-refractory cases leave doctors and patients locked in a stalemate. An olfactory implant (OI), in analogy to the widely successful cochlear implant, still seems far away from realization. The present study sought to evaluate the demand of OI in patients with OD.

**Methods:** Sixty-one patients (28 females and 33 males, mean age/standard deviation 54.9/17.6 years) with OD were recruited. We performed olfactory testing for threshold (T), discrimination (D), and identification (I) using Sniffin’ Sticks; summed scores (TDI) allowed us to determine normosmia, hyposmia, and anosmia. We applied questionnaires on the importance of smell (IOS), on olfactory disorders (QOD) and on the interest/willingness for OI, considering the need for skull base/ head surgery.

**Results:** Twenty-one patients (34.4%) stated that OI could be a future treatment option for them. This decision significantly correlated with TDI, I, complaint-related questions of the QOD, and IOS (P < .05).

**Conclusion:** With approximately one-third of patients considering OI as a therapy option, this study seems to indicate a demand for OI. In selected patients, with a high degree of complaints, low olfactory test scores, and maybe an additional occupational need for olfactory function, OI might be an option if future developments warrant safety of OI procedures.

**Key Words:** Anosmia, hyposmia, olfactory implant, therapy, questionnaire.

**Level of Evidence:** 4

Laryngoscope, 129:312–316, 2019

**INTRODUCTION**

The sense of smell, despite its important contribution to flavor perception, is commonly regarded to be inferior to other senses such as seeing or hearing. But once olfactory dysfunction (OD) is noticed, sense of smell can play a significant role in daily life and have an impact on its quality. OD can contribute to the development of depression. It affects working life (e.g., perfumers, cooks), perception of potentially dangerous situations (e.g., spoiled food, hygiene problems), or social communication.

The true prevalence of OD is an issue in research considering that not all patients with OD seek medical help. In 1,387 randomly selected Swedish individuals, Brämerson et al. found a prevalence of almost 20% OD and a rising probability of OD with increased age and the presence of diabetes. Similar numbers were reported by Vennemann et al.

Apart from aging, the three most common causes of OD are head trauma, upper respiratory airway infections, and chronic sinusitis without or with polyposis. Infectious causes appear later in life, most frequently beyond the sixth decade. OD can also be caused by drugs or inhaled chemicals, and it may occur as a congenital condition.

Therapeutic options in OD are limited. OD associated with sinunasal disorders, such as chronic rhinosinusitis without nasal polyposis, frequently respond to steroid therapy. In posttraumatic and postviral causes of OD, the use of olfactory training has been shown. However, nonresponsiveness to therapy often leaves doctors and patients locked in a stalemate. Additionally, up to one-quarter of OD patients report a poor management of their disorder.

Olfactory implant (OI) still seems far away from realization. Nevertheless, in 2016 Constantzo and Coelho claimed patent for an OI system. Having the great success of cochlea implant in mind, the following study seeks to evaluate the demand of OI in patients with OD.

The aim of this investigation was to answer the following questions: Are patients hypothetically willing to undergo head surgery for restoring the sense of smell? If patients do consider OI, what factors influence decision making? And finally, in order to challenge seriousness of decision, would they pay for it if insurances did not cover this?
MATERIALS AND METHODS
We prospectively recruited patients with anamnestic OD through our outpatient clinic at the Medical University of Vienna (Vienna, Austria). The protocol was approved by the ethics committee of the Medical University of Vienna (EK Nr. 1032/2017) and was conducted according to the guidelines of the Declaration of Helsinki on Biomedical Research Involving Human Subjects. Data collection was performed from February 2017 to January 2018. All participants provided their written informed consent. Ear, nose, and throat examination, the patients’ history (including smoking/drinking history), and magnetic resonance imaging and/or computed tomography scan were used to determine possible reasons for olfactory dysfunction or loss.

Subjects
A total of 61 patients (28 females, 33 males, mean age/standard deviation (SD) 54.9/17.6 years) were included in this study. Most frequent reason for OD was an upper respiratory airway infection prior to OD onset (24 patients, 39.3%), followed by idiopathic causes (19 patients, 31.1%) and traumatic head injury (11 patients, 18.0%). In three cases (4.9%) OD was of sinunasal cause, in two (3.3%) of congenital, in one (1.6%) of nosuous, and in one (1.6%) of neurodegenerative. Seventeen patients (27.9%) were smokers, 15 patients (24.6%) were ex-smokers, and 29 patients (47.5%) were nonsmokers. Mean/SD duration of impairment was 28.0/46.3 months, with patients visiting our clinic at a minimum of 1 month after onset of olfactory complaints to a maximum of 18 years after onset. Thirty-four patients (55.7%) were anosmic; and 27 (44.3%) were hyposmic according to summed scores of threshold (T), discrimination (D), and identification (I) scores (see below).12

Olfactory Tests
We performed olfactory testing for T, D, and I using Sniffin’ Sticks (Burghart GmbH, Wedel, Germany). These reusable odorant “pens” were presented by a trained examiner in a forced-choice procedure. A three-alternative method was used for odor threshold and discrimination, whereas for identification four written odors were given to choose from. Summed scores (TDI) were used to differentiate between normosmic, hyposmic, or anosmic patients; higher scores suggest better olfactory function. Validated in different countries, this tool is commonly used for research.13 Results were compared with normative age-related data.12 As described by Kobal et al., normosmia can be seen at a TDI score equal or more than 31, hyposmia at more than 15 and less than 31, and functional anosmia at TDI score 15 or less.14 Investigators in this study agreed on 1 as a minimal possible score on threshold testing. Hence, we set the benchmark of anosmia at 16 or less. Patients with a score of 31 and higher did not meet inclusion criteria due to assumable normosmic function.

Questionnaires
Patients were asked whether they would consider undergoing head surgery for olfactory implant using a neurosurgical approach and if they would be willing to pay for it. Possible answers were “yes,” “no,” or “maybe.” We assessed body mass index (BMI) and estimated, in accordance to the taken medical history, the interval until physicians were consulted for olfactory dysfunction. Subjective impairment was assessed for Self-assessment of smell (SAS), Self-assessment of taste (SAT), Self-assessment of flavor perception (SAP), and Self-assessment of nasal ventilation (SAY) by using a number scale (0 = no function to 10 = perfect function). Moreover, patients were asked to estimate their reduction in quality of life. Lowered quality (LQ) due to OD (estimation in percent).

Additionally, we applied the Questionnaire of Olfactory Disorders (QOD).15 This questionnaire has been used in various studies with good reproducibility and also has been translated and validated in different languages.16,17 The used version consisted of 29 questions split into categories: four questions on parosmia, six on personality, and 19 on complaints concerning smell loss (QOD-negative statements, QOD-NS). Questions on parosmia were used to determine whether the problem lies in “smelling less” or “smelling odors differently,” with high scores indicating that odors appear different. The QOD-NS measures the subjective severity of OD. Answers were graded from 0 (not at all true) to 3 (completely true), with a maximum possible score of 57 for QOD-NS (high scores indicating high degree of complaint due to OD) and 12 for parosmia. Additionally, within the QOD, three visual analogue scales (100 mm scale ranging from 0 = no impact to 100 = very high impact) were used to assess impact of impairment on work–life (Q1), on leisure time (Q2), and on family time (Q3), with high scores indicating high disturbance on activity by impairment of olfactory function.

Finally, importance of smell (IOS) was assessed using a validated questionnaire.18 The importance of smell questionnaire consists of 19 questions graded from 0 (incorrect) to 3 (absolutely correct). Additionally, patients were able to select “cannot answer this question”; one score point then was subtracted from total points. Therefore, minimum score was minus 19 and maximum score was 57, high scores indicating high subjective IOS of smell prior to OD onset.

Statistical Analysis
Statistical analysis was performed using R Statistical Computing Software 3.4.4 (R Development Core Team, 2008, R Foundation for Statistical Computing, Vienna, Austria.) and IBM SPSS 24 (IBM Corp., Armonk, NY). The group differences were tested using Student t test and Wilcoxon signed-rank test depending on the distribution of the group values. Normality of quantitative variables was tested using Shapiro-Wilk test. Correlation analysis between QOD-NS and different variables was performed using Pearson product-moment correlation coefficient. The P value for significance was set at 0.05. GraphPrism 7.0 (GraphPad Software, Inc., La Jolla, CA) was used to visualize data.

RESULTS
Willfulness for Olfactory Implant
Fourteen patients (23.0%) considered OI as a therapeutic option; seven patients (11.4%) stated they may consider OI after further information. Gathering these two groups, assuming after introduction of OI and safety validation the maybe-group fully considers OI as a therapy option, OI could be an option for 21 patients (34.4%) (OIYes), whereas 40 patients were not willing to hypothetically undergo head surgery for OI (OINo). Fourteen patients (66.7%) of OIYes would be willing to pay for OI if insurances did not cover it. Fifteen patients (71.4%) of the OIYes group were anosmic and six patients (28.6%) hyposmic, whereas 19 patients (47.5%) of the OINo group were anosmic and 21 (52.5%) hyposmic.

Laryngoscope 129: February 2019
Besser et al.: Demand for Olfactory Implant
Olfactory Tests and Questionnaires

Mean/SD overall TDI score was 16.0/5.8, not significantly correlating with age, duration of impairment, subjective nasal ventilation, and LQ. TDI scores were significantly different between patients interested in OI and those not (see Figure 1). Mean QOD-NS score was 19.8 of 12.1 and IOS score 30.2 of 13.8, not significantly correlating with age, duration of impairment, subjective nasal ventilation, and LQ. Results of both groups (OIYes, OINo) are illustrated in Table I. There were no significant differences between groups (OIYes/No) and parosmia score and scores on personality related questions (P > .05).

Subjective SAS significantly correlated with measured olfactory function (for TDI r61 = .67, for T r61 = .57, for D r61 = .37, for I r61 = .50; P < .001, respectively). When QOD-NS is considered as a continuous variable, statistically significant correlations were found between QOD-NS and the following variables: Q1 (r56 = .57), Q2 (r61 = .65), Q3 (r61 = .54), P < .001, respectively (see also Figure 2); SAF (r55 = -.43, P < .01); and parosmia (r61 = .41, P < .05). There was no statistically significant correlation of QOD-NS with TDI (P > .05) and its subscales T, D, and I (P > .05), respectively.

DISCUSSION

The ability to smell receives more attention the more it is impaired. Among our smell and taste clinics patients, a high degree of suffering due to OD and a strong desire for new therapeutic options are evident. Their curiosity inspired our group to take a look at research progress. By the time data collection ended, no studies on olfactory implant were found on PubMed. Nevertheless, it can be expected that researchers are going to be able to restore the sense of smell, possibly using olfactory implants. Expected that researchers are going to be able to restore a high degree of suffering due to OD and a strong desire for new therapeutic options are evident. Their curiosity inspired our group to take a look at research progress. By the time data collection ended, no studies on olfactory implant were found on PubMed. Nevertheless, it can be expected that researchers are going to be able to restore the sense of smell, possibly using olfactory implants. Determining possible candidates for OI and evaluating the demand for OI appears to be of high interest.

As a major finding of this study, 34.4% of participants indicated OI as a possible therapeutic option. This percentage seems rather high, considering that such a procedure for OI would require head surgery, most likely including craniotomy. Although patients were told a neurosurgical approach might be necessary, in our cohort more patients within the OIYes group chose “Yes” rather than “Maybe.” This seems to underline the clarity of decision. Moreover, in order to challenge seriousness of the decision, we additionally asked for the willingness to pay for OI in case insurances would not cover it. Two-thirds of the OIYes patients stated they were willing to pay for OI. On the other hand, explaining surgery might involve “opening of the skull” or a “neurosurgical approach” most likely also negatively affected decision making in various cases. Furthermore, providing a “Maybe” option on OI was retrospectively too vague for certain patients and could have contributed to unresolved answers in few cases. In summary, these findings appear to reflect a demand for OI among OD patients.

Does a similar percentage of interest for OI apply for other OD patient collectives? In this cohort, patients’ characteristics (e.g., age, BMI, smoking, etiology of OD) indicated a representative sample of the average patient population visiting smell and taste clinics. Therefore, we estimate similar percentages of patients interested to undergo OI procedures in other smell and taste clinics, but not necessarily among all OD patients in other clinical settings. Many patients in the current cohort had already consulted various doctors and visited our clinic as a last resort; thus, there was an intended selection bias in the currently investigated population.

Which patients might be eligible for OI surgeries in the long run? Most of the patients within the OIYes group were anosmic. However, six patients were hyposmic. As long as subjective complaints resulting from smell

| TABLE I. | Patients’ Characteristics and Results by Groups. |
|----------|------------------------------------------------|
| OINo (n = 40) | OIYes (n = 21) |
| Age | Mean SD | Mean SD |
| 57.9 | 18.3 | 49.2 | 15.1 |
| BMI | 24.6 | 4.4 | 28.9 | 8.1 |
| T | 2.4 | 2.5 | 2.1 | 2.2 |
| D | 7.6 | 2.6 | 6.1 | 2.2 |
| I | 7.1* | 3.0 | 5.2* | 3.1 |
| TDI | 17.2* | 5.5 | 13.8* | 5.8 |
| SAS | 2.48 | 1.6 | 1.8 | 1.7 |
| SAT | 5.5 | 3.0 | 4.7 | 2.9 |
| SAF | 4.2 | 2.9 | 3.0 | 2.5 |
| SAV | 7.7 | 2.4 | 7.2 | 2.8 |
| LQ | 25.9* | 21.9 | 46.3* | 22.8 |
| IOS | 27.6* | 14.3 | 35.1* | 11.6 |
| QOD-NS | 16.6* | 9.6 | 25.8* | 14.2 |
| Q1 | 2.9 | 3.6 | 4.9 | 4.0 |
| Q2 | 4.6 | 3.4 | 6.3 | 3.2 |
| Q3 | 4.6* | 3.4 | 6.8* | 3.0 |

*Significant differences between groups (P < .05).
BMI = body mass index; D = discrimination, I = identification; IOS = Importance of smell; OD = olfactory dysfunction; OI = olfactory implant; Q1, Q2, Q3 = visual analogue scales of impairment on work-life, leisure time, and family time, respectively; QOD-NS = Questionnaire of Olfactory Disorders—negative statements; SAF = self-assessment of flavor; SAS = self-assessment of smell; SAT = self-assessment of taste; SAV = self-assessment of nasal ventilation; SD = standard deviation; T = threshold; TDI = summed T, D, and I scores; LQ = Lowered quality.
impairment are a significant disease burden, patients with residual olfactory function might be candidates for OI surgery. We know that some patients within the hyposmic range lack sufficient sensory function for daily-life olfactory experience. In case of deteriorated olfactory acuity, even these patients might benefit from OI after several years of waiting to regain olfactory function.

Another issue of ongoing research is depression and its impact on olfactory function. It has not been specifically addressed in this investigation. Depression does not appear to uniformly affect smell function, but that olfactory impairment is more related to course and duration than severity of depression. Furthermore, increased olfactory function in patients suffering from olfactory disorders was shown to be linked to an improvement in quality of life and state of depression. In consequence of these interactions, future research on eligibility for OI should include detailed examination of patients’ depression state.

Which factors influenced the decision in our cohort regarding OI? First, the decision was influenced by the severity of complaints of OD. Patients tended to choose OI the higher the QOD-NS scores. Secondly, the subjective IOS might have contributed to decision making. The higher IOS scores were, the more likely patients considered OI as a possible therapeutic option. However, compared to the majority of our participants, two patients with congenital anosmia (both within OINo group) stated low scores on IOS (minus 17 and 9) and QOD-NS (7 and 9). The sense of smell did not appear very important to these patients, in concordance to previous findings. They had never experienced smell perception and probably therefore stated low IOS and a low degree of complaints. When excluded, the correlation of IOS, as well as QOD-NS and decision making, did not reach significance. Thirdly, olfactory testing score influenced decision for OI. The lower the mean Identification and TDI score, the more likely patients considered OI as a possible therapy option. This indicates the use of olfactory tests is a valuable tool to select possible candidates and predict the decision for OI. The QOD-NS and IOS can be of additional help to isolate possible candidates, at least in non-congenital OD patients. However, further studies on other factors (e.g., depression, other comorbidities) will be needed to help identify OI candidates with serious intentions and realistic expectations.

Although the QOD has been proven as an adequate tool in various studies, within our cohort just assessing Q1, Q2, and Q3 appeared to be sufficient to predict a high QOD-NS score (see also Figure 2). Questions on work-life, leisure time, and family time seem to cover most complaint themes. Assessing Q1, Q2, and Q3 alone would be less time-consuming; and for various questions, with limitations, it may be as conclusive as QOD-NS, although the use of these three questions by themselves of course awaits formal analysis. Also, high subjective flavor perception impairment contributed to a high degree of complaint, as seen in a negative correlation of QOD-NS and SAF.

Within our cohort, TDI scores significantly correlated with SAS but not with QOD-NS. Olfactory function was quite adequately “foreseen” by our patients, as indicated by subjective ratings (SAS) prior to olfactory testing. The degree of complaint, however, not only within our cohort, varies and does not reflect olfactory capacity. Inconsistent subjective scoring in relation to olfactory measurements can be found in the literature. Interestingly, one subject stated OI as a possible therapy option, scored relatively high on IOS (49), and had the highest TDI score (28.75) of all participants. This could be a coincidence but also brings to the surface the impact of subjective smell importance on the degree of impairment, regardless of test results. At our clinic, patients frequently are desperate, although they are “just” slightly hyposmic, whereas others appear to compensate anosmia quite well. We therefore think it would be useful, beside appropriate olfactory testing, to assess IOS, QOD (at least Q1,2,3), and SAS on a regular basis in patients with OD. Additionally, standardized psychological examination might be useful to obtain an overall picture of the severity of the disease.

CONCLUSION

The impairment of olfactory function strongly affects our patients’ daily life. In this selected cohort, depending on the degree of complaints and olfactory test scores, one-third of all patients would consider olfactory implant as a possible therapy option even if skull base/head surgery was necessary. In selected patients with a high degree of complaints, low olfactory test scores, and perhaps an additional occupational need for olfactory function, OI might be an option if future developments warrant safety of OI procedures. Research on OI is needed because this study clearly demonstrates a demand for it.

BIBLIOGRAPHY

1. 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.
2. Crov I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. Chem Senses 2014;39:185–194.
3. Brämerson A, Johansson L, Ek L, Nordin S, Bende M. Prevalence of olfactory dysfunction: the Skövde population-based study. Laryngoscope 2004;114:733–737.
4. Vennemann MM, Hummel T, Berger K. The association between smoking and smell and taste impairment in the general population. J Neurol 2008;255:1121–1126.
5. Park T, Hummel T. Olfactory disorders: distribution according to age and gender in 3,400 patients. *Eur Arch Otorhinolaryngol* 2013;270:777–779.

6. Temmel AFP, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. *Arch Otolaryngol Head Neck Surg* 2002;128:635–641.

7. Damn M, Pikart LK, Reimann H, et al. Olfactory training is helpful in post-infectious olfactory loss: A randomized, controlled, multicenter study. *Laryngoscope* 2014;124:826–831.

8. 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.

9. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. *Rhinology*. 2017;55:17–26.

10. Landis BN, Stow NW, Lacroix JS, Hugentobler M, Hummel T. Olfactory disorders: the patients’ view. *Rhinology* 2009;47:454–459.

11. Coelho D, Park T, Abdel-Hamid M, Costanzo R. The olfactory implant system: a novel method to treat anosmia. 17th International Symposium on Olfaction and Taste (ISOT2016). *Chem Senses* 2016;41:e263.

12. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the “Sniffin’ Sticks” including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol* 2007;264:237–243.

13. Hummel T, Whitcroft K, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinol Suppl* 2017;54:1–30.

14. Kohal G, Klimek L, Wollensberger M, et al. Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. *Eur Arch Otorhinolaryngol* 2000;257:205–211.

15. Frasnelli J, Hummel T. Olfactory dysfunction and daily life. *Eur Arch Otorhinolaryngol* 2004;262:231–235.

16. Simopoulos E, Katotomichelakis M, Gouveris H, Tripsianis G, Livaditis M, Danielides V. Olfaction-associated quality of life in chronic rhinosinusitis: adaptation and validation of an olfaction-specific questionnaire. *Laryngoscope* 2012;122:1450–1454.

17. Jalesi M, Kamrava SK, Amini E, et al. Is the Persian version of the “Olfactory Disorder Questionnaire” reliable and valid? *Iranian J Otorhinolaryngol* 2017;29:209–213.

18. Croy I, Buschhüter D, Seo H-S, Negoias S, Hummel T. Individual significance of olfaction: development of a questionnaire. *Eur Arch Otorhinolaryngol* 2009;267:67–71.

19. Rochet M, El-Hage W, Richa S, Kazour F, Atanasova B. Depression, olfaction, and quality of life: a mutual relationship. *Brain Sci*. 2018;8:80.

20. Croy I, Hummel T. Olfaction as a marker for depression. *J Neurol* 2017;264:631–638.

21. Pabel LD, Hummel T, Weidner K, Croy I. The impact of severity, course and duration of depression on olfactory function. *J Affect Disord* 2018;238:194–203.

22. Katotomichelakis M, Simopoulos E, Tripsianis G, et al. Improvement of olfactory function for quality of life recovery. *Laryngoscope* 2013;123:1108–1116.

23. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses* 2003;28:691–694.