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Olfactory training in long COVID-19 patients with lasting symptoms including olfactory dysfunction

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ABSTRACT

INTRODUCTION. Two-thirds of patients with COVID-19 developed smell and taste dysfunction, of whom half experienced improvement within the first month. After six months, 5-15% still suffered from significant olfactory dysfunction (OD). Before COVID-19, olfactory training (OT) was proved to be effective in patients with post-infectious OD. Therefore, the present study aimed to investigate the progress of olfactory recovery with and without OT in patients with long COVID-19.

METHODS. Consecutive patients with long COVID-19 referred to the Flavour Clinic at Gødstrup Regional Hospital, Denmark, were enrolled. The diagnostic set-up at the first visit and follow-up included smell and taste tests, questionnaires, ENT examination and instructions in OT.

RESULTS. From January 2021 to April 2022, 52 patients were included due to long COVID-19-related OD. The majority of patients complained of distorted sensory quality, in particular, parosmia. Two-thirds of the patients reported a subjective improvement of their sense of smell and taste along with a significant decline in the negative impact on quality of life ($p = 0.0001$). Retesting at follow-up demonstrated a significant increase in smell scores ($p = 0.023$) where a minimal clinically important difference (MCID) in smell scores was found in 23% of patients. Full training compliance was significantly associated with the probability of MCID improvement (OR = 8.13; $p = 0.04$).

CONCLUSIONS. The average effect of OT is modest; however, full training compliance was significantly associated with an increased probability of a clinically relevant olfactory improvement.

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A considerable proportion of patients with COVID-19 develop persisting symptoms after recovery from their initial infection. A striking 87% of hospitalised COVID-19 patients still suffered from at least one sequela after 60 days, and 35% experienced long-lasting symptoms [1]. Moreover, a multitude of studies have suggested that 10% of patients with COVID-19 experience sequelae such as fatigue, anxiety, dyspnoea, cognitive problems and olfactory dysfunction (OD) [1-3]. As a consequence, WHO has defined long COVID-19 as persisting symptoms for more than 12 weeks after the onset of COVID-19 [4].

OD, i.e. complete loss (anosmia), reduction (hyposmia) and/or smell distortions (parosmia and phantosmia), is common after COVID-19 [1-7]. The duration of OD differs considerably. One study found that 88% of patients

regained their olfactory function after two months, whereas the remaining 12% suffered from long-term OD [3]. A particular feature of post-COVID-19 OD is long-lasting parosmia and/or phantosmia in two-thirds of the patients, often with delayed debut several months after the initial infection [6]. Our own data on patients who reported OD outcomes more than one year after COVID-19 revealed that 42% of respondents reported sustained complete recovery, 41.7% reported partial recovery and 2.4% reported no olfaction improvement. Furthermore, parosmia was indicative of prolonged recovery [7].

No specific treatment of OD in patients with long COVID-19 has been presented. The results of administration of corticosteroids and/or various vitamins are either contradictory or unconvincing [8-11]. Prior to COVID-19, olfactory training (OT) has proven to be a promising method in post-infectious OD. Thus, in a systematic review of controlled studies on OT, Kattar N et al. found that a minimum clinically relevant effect was seen in 28-71% of patients where post-viral aetiology, short duration of OD and OT for more than 3-4 months were positive predictors [12]. Accordingly, various guidelines for treatment of COVID-19 OD recommend OT as the first priority [13-15]. With regard to parosmia, a recent retrospective study demonstrated a positive effect of OT among patients with post-infectious non-COVID-19 OD [16].

It remains unknown if OT is beneficial in patients with combined OD and other post-COVID-19 sequelae, i.e. long COVID-19 [17, 18].

The purpose of this study was to investigate OT and prognostic factors for subjective and measured olfactory function in patients with long COVID-19.

METHODS

As from January 2021, patients with long COVID-19 (ICD10 code: DB948A) were referred to the Flavour Clinic, Gødstrup Regional Hospital, Denmark [19], from the two regional long COVID-19 hospital clinics [2, 4].

At baseline, the Sino-nasal outcome test (SNOT-22), the Major Depression Inventory (MDI) and demography questionnaires were administered. The influence of OD on quality of life (QoL) was assessed by a ten-point visual analogue scale (1 = no influence; 10 = worst possible influence). Furthermore, a Mini Mental State Examination (MMSE) was conducted mainly in patients older than 50 years. The orthonasal olfactory function was tested by the psychophysical Sniffin' Sticks TDI test (Burghart), which consists of a threshold test (T), a discrimination test (D) and an identification test (I). The taste spray test was used to screen the patient's ability to identify sweet, salty, sour and bitter tastants. An ENT examination including nasal endoscopy was conducted, and, finally, the patients were instructed in OT. Due to ethical concerns, we gave all referred patients the possibility of OT instead of using a randomised controlled trail (RCT) design. The training programme consisted of smelling four different odorants (essential oils) twice a day for at least three to four months. The patients needed to purchase the oils themselves. The patients also received a link to an OT video instruction.

Patients were invited for follow-up visits at three- to four-month intervals, at which the baseline questionnaires and tests were re-administered. Training compliance was registered as 0 (no training at all), 1 (partial training, i.e., not following the given instructions with respect to frequency or duration), or 2 (according to instructions).

Patients lost to follow-up, patients with a second COVID-19 episode before the first follow-up visit and patients participating in research protocols involving interventions with potential effects on smell and taste were excluded from the study.

During clinical visits, participants were given detailed information about all testing procedures and gave written consent for data storage and usage for future research. Storage of data was approved by the Danish Data Protection Agency.

Statistics

Data were analysed using JMP Pro 16. Pearson&;s χ^2 test was used for evaluating differences in categorical variables between all groups. Normal distribution was assessed using QQ-plots and the Shapiro-Wilk W test. In parametric data, mean values were compared using student's t-test and presented as means with 95% confidence interval (CI). Odds ratios (OR) were used to calculate prognostic factors of recovery between OT compliance groups, whereas ANOVA and Spearman's were used to analyse correlations. The α level of statistical significance was set at 0.05.

Data sharing

The data upon which the findings of this study were based are available from the corresponding author upon reasonable request.

*Trial registration: n*ot relevant.

RESULTS

From January 2021 to April 2022, a total of 71 patients with long COVID-19 OD were referred to the Flavour Clinic. Six patients had a second COVID-19 incidence before follow-up and nine patients only accepted follow-up by phone. Three patients did not attend the follow-up visit and one patient participated in a research study on extended smell training. Thus, at least one follow-up visit was completed in 52 patients. Fifteen patients had two follow-up visits. All patients suffered from qualitatively disturbed olfaction, i.e. parosmia and/or phantosmia, and more than half of the patients indicated experiencing a severe impact on their QoL ($\geq$ 7 of 10). SNOT-22 scores varied considerably, especially due to the subscores loss of smell, tiredness and sleep disturbances. MDI scores were variable, as 20% had scores indicating moderate to severe depression. Finally, one patient had an MMSE score below 24 indicative of mild cognitive impairment (**Table 1**).

TABLE 1 Demographics and baseline measures at inclusion of patients with physical follow-up (N = 52).

Age, median (range), yrs	47 (15-71)
Females, %	71.1
Smokers, current/former, %	11.5/15.4
Healthcare worker, %	39.2
Upper airway allergy, %	43.1
No comorbidity prior to COVID-19, % of patients	32.7
Duration of OD, median (range), mos.	8 (3-18)
Other long-term COVID-19 sequelae[a], median (range), n	4 (1-5)
Hospital admission due to COVID-19, %	17.3
SNOT-22, median (range), points	31 (10-75)
MDI, median (range), points	17 (0-42)
MMSE score, median (range), points	28 (23-30)

MDI = Major Depression Inventory (scale 0-50 points); MMSE = Mini Mental State Examination t(scale 0-30 points); OD = olfactory disorders; SNOT-22 = Sino-Nasal-Outcome Test (scale 0-110 points).
a) Tiredness, headache, cognitive problems, respiratory symptoms, muscle/joint symptoms, sensibility disturbances, cardiac symptoms, skin rash, hyperacusis/tinnitus, photo sensibility, dizziness, throat pain, oral pain, weight loss, hearing loss/tinnitus, sleep problems, psychiatric problems.

Overall, OD had a moderate to major impact on the patients' QoL. Although patients with complaints of a distorted sense of smell rated a slightly larger negative impact on QoL, this difference was not significant (mean difference 0.59; p = 0.43).

Two-thirds of patients experienced subjective improvement/normalisation of their smell and taste function over time, and simultaneously the impact of OD on QoL tended to decline (**Table 2**).

TABLE 2 Subjective and objective measures at baseline and follow-up.

		Physical follow-up		
	Baseline visit (N = 52)	**1st (n = 52)**	**2nd (n = 15)**	**last (n = 52)**
Duration since COVID-19 onset, median (range), days	261 (23-607)	425 (127-750)	524 (330-725)	485 (228-750)
Subjective sense of smell, n (%)				
Reduced	52 (100)	47 (90.4)	13 (85.7)	45 (86.5)
Distorted	40 (76.9)	36 (69.2)	9 (60.0)	32 (61.5)
Subjective sense of smell, n (%)				
Reduced	43 (82.7)	31 (59.6)	6 (40.0)	28 (53.8)
Distorted	36 (69.2)	24 (46.2)	4 (26.7)	14 (26.9)
Olfactory test score, mean (95% CI), points				
TDI[a]	25.1 (23.2-26.9)	26.5 (24.6-28.5)	23.9 (17.7-30.2)	26.5 (24.5-28.5)
T	3.6 (3.0-4.3)	4.5 (3.8-5.2)	4.0 (3.1-4.9)	4.4 (3.7-5.1)
D	9.9 (9.1-10.7)	10.2 (9.4-11.0)	11.9 (10.7-13.1)	10.4 (9.5-11.3)
I	11.5 (10.7-12.4)	11.8 (10.9-12.8)	12.9 (11.9-14.0)	11.7 (10.8-12.7)
Taste spray score, mean (95% CI), n[b]	3.74 (3.53-3.95)	3.76 (3.55-3.97)	3.77 (3.41-4.13)	3.74 (5.53-3.95)
Impact of OD on QoL on a 10-point VAS, mean (95% CI)	6.55 (5.93-7.17)	5.62 (4.90-6.34)	5.00 (3.89-6.11)	5.42 (4.77-6.08)
OT compliance since previous visit, n (%)				
0	-	6 (11.5)	7 (47.1)	12 (23.1)
1	-	15 (28.8)	1 (5.9)	12 (23.1)
2	-	31 (59.6)	7 (47.1)	28 (53.8)
Subjective smell since last visit, n (%)				
No improvement	-	17 (32.7)	4 (26.7)	16 (30.8)
Improvement[c]	-	30 (57.7)	8 (53.3)	28 (53.8)
Normalisation	-	3 (5.8)	1 (6.7)	5 (9.6)
Deterioration	-	2 (3.8)	2 (13.3)	3 (5.8)
Subjective taste since previous visit, n (%)				
No improvement	-	16 (30.8)	3 (20.0)	17 (32.7)
Improvement[c]	-	24 (46.2)	5 (33.3)	21 (40.4)
Normalisation	-	10 (19.2)	6 (40.0)	13 (25)
Deterioration	-	2 (3.8)	1 (6.7)	1 (1.9)

CI = confidence interval; OD = olfactory disorders; OT = olfactory training; QoL = quality of life; TDI = threshold-discrimination-identification; VAS = visual analogue scale.
a) Sniffin' Sticks TDI test (Burghart) (scale 1-48 points).
b) Correct answers out of 4 tastes: salt, sweet, sour, bitter.
c) Reflects the improvement since previous clinical evaluation, not improvement or deterioration overall.

Patients had improved olfactory test scores from the initial visit to the final visit with a mean improvement of 1.42 in the total TDI score (paired t-test, 95% CI 0.20-2.6; p = 0.02), which is below the minimal clinically important difference (MCID) of 5.5. In total, 33 patients improved TDI scores, 12 patients (23.1%) had an improvement of ≥ 5.5 (range: 5.5-12) and only one patient had a deterioration of ≥ 5.5 (score: –6).

Parosmia was reported by 77% of patients, with no significant difference in TDI improvement (p = 0.57) between parosmic and non-parosmic patients.

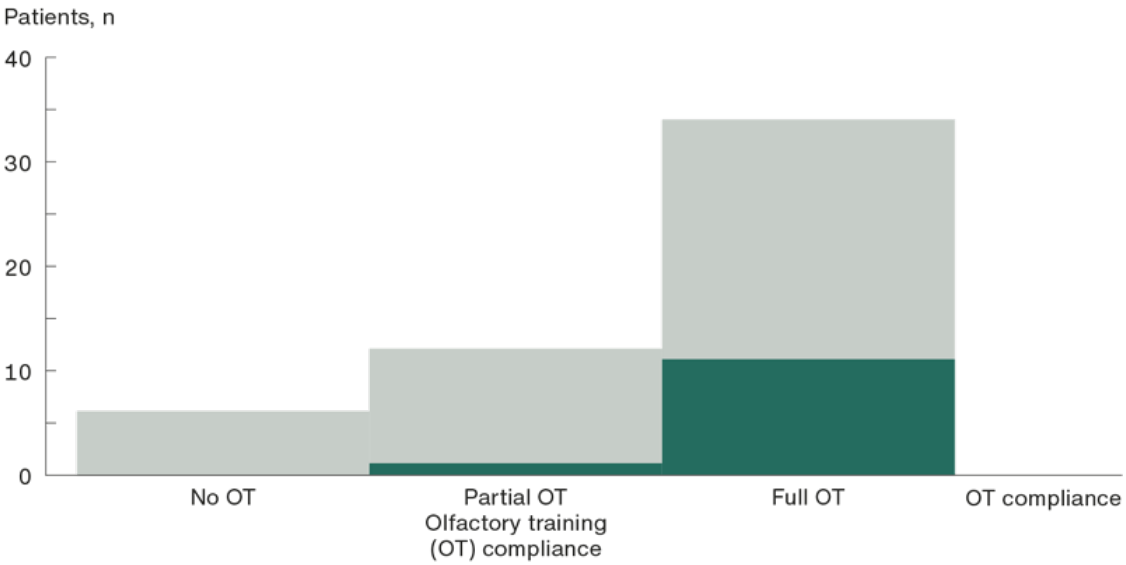
The negative effects of OD on QoL decreased over time (paired t-test, mean difference –1.1; p = 0.0001). The ratings of olfactory-specific QoL were not significantly correlated with TDI scores, either at the initial visit (Spearman's = 0.071; p = 0.62) or at the final visit (Spearman's = –0.09; p = 0.53).

An increased number of other long COVID-19 sequelae other than taste and smell deficits was not correlated with a poorer TDI score at the initial (ANOVA, F = 1.42; p = 0.24) or final visit (ANOVA, F = 1.67; p = 0.17). The number of other long COVID-19 sequelae was not significantly associated with the subjective negative impact of OD on QoL at the initial (χ^2 = 0.37; p = 0.54) or the final visit (χ^2 = 0.90; p = 0.34).

Although patients with full OT compliance did not show a significant mean TDI score improvement (t-test, p =

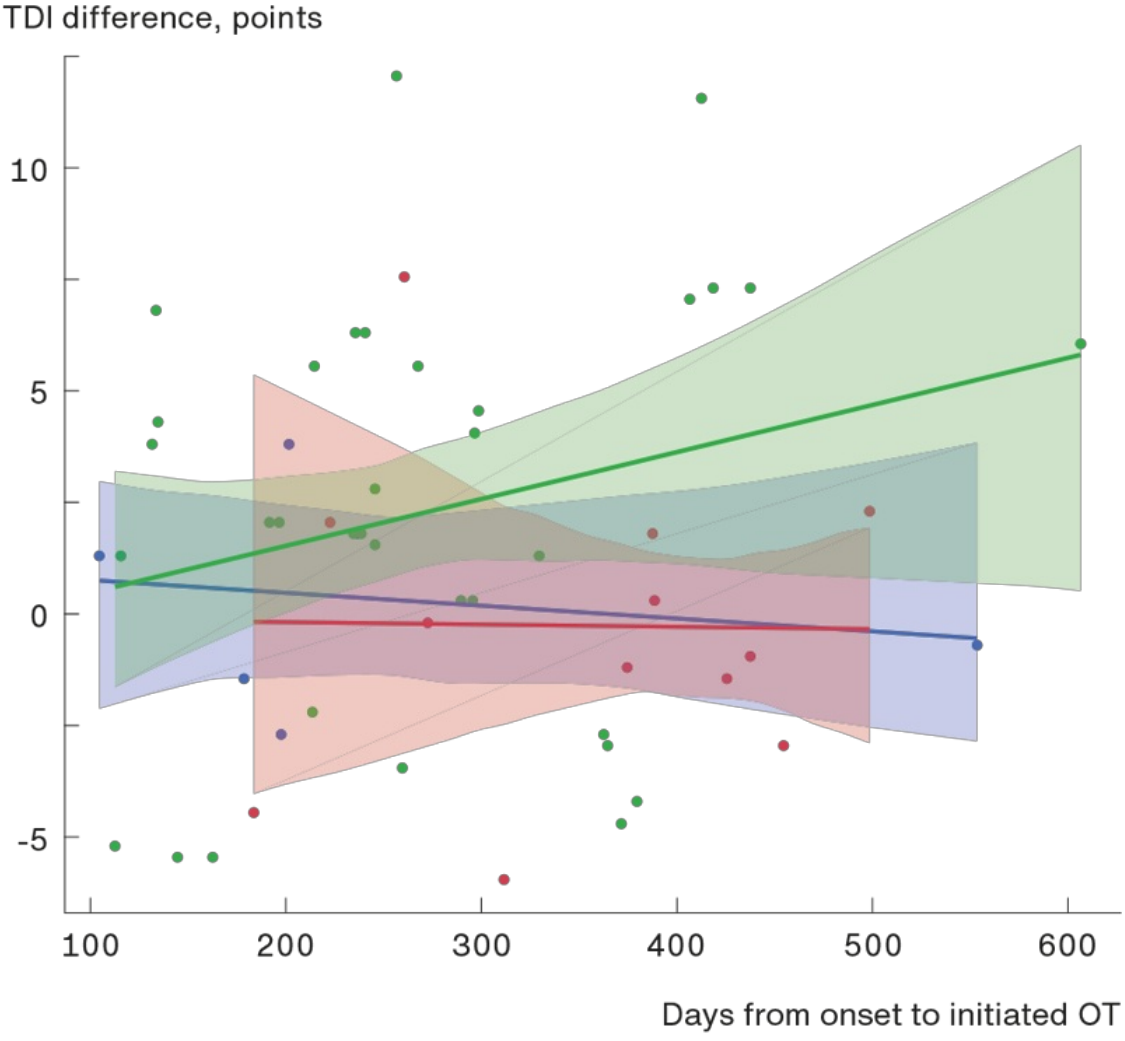
0.37), MCID improvement was associated with full compliance (p = 0.04). Among the 12 patients with MCID, 11 had full OT compliance. As such, full compliance was associated with increased probability of achieving a clinically relevant TDI improvement of 5.5 or more: OR = 8.13 (95% CI: 0.96-69.17) (**Figure 1**). Age, baseline TDI and duration of OD had no significant influence on the chance of achieving a TDI improvement of 5.5 or more. Notably, patients with a long OD duration did not experience less effect of OT than other patients (**Figure 2**).

FIGURE 1 Olfactory training (OT) compliance was significantly associated with minimal clinically important difference (MCID) improvement of olfactory test scores (TDI ≥ 5.5). Distribution of MCID improvement in dark green highlights the significant association between improved olfactory function and OT (p = 0.04).



TDI = threshold-discrimination-identification.

FIGURE 2 TDI difference from the initial visit to last clinical control (mean, confidence of fit) in relation to the duration of olfactory dysfunction and compliance with olfactory training (OT). Compliance: blue (0 = no OT), red (1 = partial OT), green (2 = OT twice daily for ≥ 3 months during the follow-up period).



TDI = threshold-discrimination-identification.

DISCUSSION

We found that in patients with long COVID-19, two-thirds experienced subjective improvement or normalisation of their sense of smell and taste and a reduced negative impact on QoL. In total, 63% of the participants achieved some improvement of their TDI scores. In general, the effect of OT was modest as only 23% achieved a MCID in TDI scores of at least 5.5. However, we identified an association between compliance and MCID ($p = 0.04$), where full training compliance increased the odds of MCID improvement (OR = 8.13).

A systematic review of OT on post-infectious OD found MCID improvement among 28-71% of patients [12]. The studies included in the review were prospective controlled cohort studies and RCTs. Thus, we expected similar improvement in patients with long COVID-19, as they met the same criteria of age, duration of OD, viral aetiology and training paradigm [12]. The number of patients included in the present study is comparable to the study populations in the review. However, only 23% of our cohort experienced an MCID of 5.5 or more. Among the few studies of OT in patients with COVID-19, Le Bon et al. also found a modest effect of OT on mean TDI scores (a mean improvement of 2.1) and did not report MCID in their pilot study [17]. Altundag et al. also demonstrated increased TDI scores, and OT enhanced the improvement significantly [18].

Full training compliance was the only prognostic factor associated with olfactory improvement in the present study. Unfortunately, details on training compliance are rarely reported. In the pilot study by Le Bon et al. on oral corticosteroids and OT in a total of 27 patients with COVID-19 (only OD and not long COVID-19), the authors found full compliance in 31% to 43% in contrast to 54% in our study [17]. Our data on compliance were self-reported and may potentially be overestimated. Thus, the difference in outcome of OT between our and other studies may be due to the percentage of patients with full training compliance.

In line with other findings, the major complaint among patients with long COVID-19 was distortion of the senses rather than quantitative problems (hyposmia or anosmia), which, in contrast, is the most common complaint for non-COVID-19 post-infectious OD [12, 16, 18]. Parosmia and phantosmia are subjectively perceived experiences for which there is no clinical test. In line with other studies, we found increased TDI scores over time in patients with long COVID-19 suffering from parosmia. However, this may not reflect an improvement of sensory distortion [16-18].

Whereas previous studies have reported diverging results [8, 12, 16-18], neither age, gender, duration of OD, TDI at baseline or other long COVID-19 sequelae were correlated with the OT effect in the present study.

We used the median value of eight months of OD as cut off in the calculation of correlations between OD duration and improvement and the minimum duration of OD was three months. As we have shown in earlier studies, the spontaneous recovery of OD is much more frequent in the first three months after COVID-19 infection [8, 20]. However, we found that patients with delayed onset of OT did not show less improvement during the follow-up period. The findings of the present study may differ in patients with a shorter OD duration. Perhaps enhanced improvement can be achieved with earlier onset of OT during the period of more frequent spontaneous recovery. However, this is beyond the scope of this study.

Our study as well as previous studies carry limitations due to selection bias, confounders, study design, population size, dropouts/loss to follow-up and patient reports on compliance. We lost 19/71 (27%) at follow-up, mainly due to new COVID-19 episodes and unwillingness to spend time on follow-up. Furthermore, given the observational design, we can only report an association between OT and MCID improvement. It may be hypothesised that patients with olfactory improvement are more motivated for conducting OT than patients without olfactory improvement. Future randomised studies are warranted to confirm causality.

CONCLUSIONS

At present, OT is often the only olfactory treatment option in patients with OD after COVID-19. Albeit the overall average effect of OT was modest, full OT compliance was significantly associated with eight-fold higher odds of MCID improvement. However, further randomised studies are needed to confirm causality.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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