Treatment adherence to olfactory training: a real-world observational study*

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Abstract

Background: Olfactory training (OT) is considered an effective intervention for most causes of smell loss and is recommended as a long-term treatment. However, the treatment adherence of OT remains unclear. This study aims to identify the frequency and causalities for lack of adherence to OT.

Methods: In this prospective study, 53 patients previously diagnosed with olfactory dysfunction (OD), who were recommended to perform OT, were enrolled. Patients underwent olfactory testing using Sniffin' Sticks for threshold, discrimination, and identification (TDI) and a subjective numeric rating scale (NRS) at a baseline and follow-up visit. In addition, patients answered a six-item treatment adherence questionnaire. The primary outcome measures were clinically relevant improvements according to the TDI (≥5.5) and NRS (≥1) scores.

Results: Out of 53 patients, 45 performed OT. Among patients who performed OT, 31% discontinued the use of OT on their own due to a self-perceived improvement, while 51% discontinued use due to lack of improvements in olfaction. In these patients, the average duration of OT use was five months. After controlling for baseline duration of OD, baseline TDI score and smell loss aetiologies, discontinuing OT due to a lack of self-perceived improvement remained significantly associated with worse TDI and NRS outcomes at follow-up.

Conclusions: Our data show that therapeutical adherence to OT is low, regardless of patients' perception of olfactory function. Olfactory improvement leads to decreased training due to satisfaction, while lack of improvement leads to non-adherence based on disappointing subjective outcome. Patients should be advised to perform OT consistently.

Key words: olfactory training, olfaction disorders, treatment adherence and compliance, smell, patient reported outcome measures

Introduction

Olfactory dysfunction (OD) significantly impacts the quality of life and impairs one's ability to recognize hazards such as spoiled food, gas leaks or fire [1,2]. Many aetiologies, including viral infection, traumatic injury, sinonasal obstruction and neurodegenerative diseases, can result in smell loss. Yet, up to one-sixth of affected patients suffer from idiopathic OD [3]. While OD patients with sinonasal or systemic diseases can benefit from treatment of the underlying condition, those presenting with smell loss not associated with a treatable disease are more challenging to treat. Medical treatment options include intranasal and oral corticosteroids, intranasal sodium citrate and oral zinc supplementation. However, evidence on the clinical benefit of these interventions is generally poor [4]. Therefore, olfactory training (OT) remains the current gold-standard treatment for most causes of OD, including post-viral, post-traumatic and idiopathic smell loss [4-6].

OT consists of four scent oils recommended to be used twice daily. Classical OT as proposed by Hummel et al. [7] is comprised of four oils from different categories of scents (floral, fruity, resinous, and aromatic). Interestingly, subsequent studies of modified regimens have shown that varying choices and sources

of odours (e.g., patient-purchased essential oils or household scents) do not appear to affect the outcome when compared to classical OT [8-11]. Recommended time of use in the current literature is at least three months, although longer regimens of up to a year have shown additional benefit, making it a long-term therapy [12,13]. The extended course of treatment and the generally slow recovery of olfactory function can affect patients willingness to perform OT consistently, resulting in high drop-out rates of up to 45% [14]. The importance of treatment adherence is well documented in other rhinological conditions, such as chronic rhinosinusitis (CRS) and allergic rhinitis. Phillips et al. reported generally low adherence rates to intranasal corticosteroid sprays and saline irrigation of below 50% in CRS patients [15]. Similarly, Hosoya et al. reported poor adherence to dupilumab injections in 30% of patients in a mixed cohort of CRS with nasal polyposis, atopic dermatitis and bronchial asthma cases [16]. A large-scale study of allergic rhinitis patients showed that out of over 100,000 patients treated with sublingual and subcutaneous immunotherapy, one-year adherence rates were, at most, 65%, with particularly low adherence rates of less than 30% for sublingual immunotherapy [17]. These findings highlight the pervasive challenge of treatment adherence in long-term therapies of rhinological conditions.

Although OT is internationally established [18-20], little is known about its treatment adherence. A prospective trial of 25 patients has shown adherence rates of 56% at the six-month mark [21]. However, there is need for more real-world evidence on OT adherence and its implications for treatment success. Gaining more insight into treatment adherence is crucial, as it might help clinicians to improve therapy outcomes by spending more time on patient education and recommending closer follow-ups to monitor OT use.

Therefore, this prospective study aimed to analyse OT adherence and its impact on objective and subjective improvement of olfactory function in a real-world setting. We investigated several dimensions of adherence that could affect long-term use and lead to early treatment discontinuation.

Materials and methods

Study population

This prospective, cross-sectional, single-centre study enrolled 53 patients previously diagnosed with OD at our specialized outpatient smell and taste clinic between January 2011 and October 2020 (Supplementary Figure 1). Clinical characteristics of the study cohort are provided in Table 1. At the baseline visit, patients had already suffered from OD for an average of 29 (range: 9-204) months. The average duration between visits was 36 (range: 10-115) months.

Study design

Participants were recruited by postal invitation to all patients, who visited our clinic between 01.01.2017 and 31.12.2020 for an initial or follow-up visit. All patients were instructed to perform OT. Inclusion criteria were: 1) post-viral, post-traumatic or idiopathic aetiology for OD; 2) OD at baseline defined as TDI<30.5; 3) documented prescription of OT at baseline; 4) completed questionnaire of treatment adherence at follow-up (all patients were called in for a second visit to undergo objective olfactory testing and complete the questionnaire). Smell loss aetiology was diagnosed according to the European position paper on olfactory disorders [22].

Ethics approval and consent to participate

The study was approved by the ethics committee of the Medical University of Vienna (Approval number: 2052/2019). Written informed consent was obtained from all subjects prior to participation.

Olfactory training

The attending otorhinolaryngologist instructed all patients to perform OT using four different, patient-purchased scented oils. The prescribed odours included one or two fruity, one or two flowery and one resinous odour. In addition, written handouts were provided on how to perform OT. Patients were recommended to perform OT for at least 12 months by consciously smelling each scented oil for at least 30 seconds twice daily (morning and evening). Attention was drawn to the importance of resealing scented oil containers to avoid loss of smell potency.

Olfactory testing

Objective olfactory function was performed using the Sniffin' Sticks test to assess olfactory threshold, discrimination and identification (TDI) function [23]. The minimal clinically important difference (MCID) was set to 5.5 [24]. Patients who yielded a TDI score higher than the MCID at follow-up, were considered as having objectively improved olfactory performance. Subjective olfactory function was assessed using a self-reported numeric rating scale (NRS) from 0 ("very bad") to 10 ("very good"). Patients who reported an NRS improvement of ≥1 were considered to have improved subjective olfactory function [25].

Questionnaire of Treatment Adherence

Patients answered a questionnaire regarding their treatment adherence to OT during their follow-up visit. The questionnaire included six items in the German language regarding treatment consistency, cause for discontinuation of treatment, time until discontinuation of treatment, perceived tediousness, and forgetfulness (Supplementary Table 1 and 2).

Statistical analysis

TDI and NRS differences between patients with and without OT, and differences in duration of use between patients, who

Table 1. Study population.

Variables	n (total)						
Age	53	n	Mean	SD	Min	Max	Median
in years old		53	60.60	14.89	24	83	63
Sex	53	n	%				
Male		28	52.83				
Female		25	47.17				
Cause of smell loss	53	n	%				
Post-traumatic		7	13.21				
Post-viral		23	43.40				
Idiopathic		23	43.40				
Duration of OD at baseline	53	n	Mean	SD	Min	Max	Median
in months		53	29.25	46.48	0	204	9
Average follow-up period	53	n	Mean	SD	Min	Max	Median
in months		53	36.05	16	10	115	34
TDI at baseline	53	n	Mean	SD	Min	Max	Median
		53	15.83	5.99	2	27.5	15.75
TDI at follow-up	53	n	Mean	SD	Min	Max	Median
		53	17.62	7.63	4	33.25	17.75
NRS at baseline	53	n	Mean	SD	Min	Max	Median
		53	1.92	1.04	1	5	2
NRS at follow-up	53	n	Mean	SD	Min	Max	Median
		53	3.06	2.37	1	10	2
TDI improvement	53	n	%				
No		41	77.36				
Yes		12	22.64				
NRS improvement	53	n	%				
No		32	60.38				
Yes		21	39.62				

stopped OT due to improvement or non-improvement, were analysed using unpaired t-tests. Differences in TDI and NRS between smell loss aetiologies were analysed using one-way analysis of variance and multiple comparison testing using Dunnett's correction. Furthermore, discrepancies in responses to the OT adherence questionnaire between different aetiologies were analysed using the Fisher's exact test. Improvements in TDI and NRS were investigated using univariable and multivariable binary logistic regression. Multivariable models were corrected for clinically relevant confounders (age, gender, aetiology, duration of OD at baseline, and baseline TDI), and significant items from the treatment adherence questionnaire. When binary logistic regression was inappropriate due to the independent variable's perfect prediction of the dependent variable, the independent variable was dropped from regression analysis and instead analysed using the Fisher's exact test. The confidence interval was set to 95% and results with a p-value ≤0.05 were considered statistically significant. Statistical analysis was performed using STATA (Version 14, StataCorp LLC, TX, USA) and GraphPad Prism (Version 9, Graphpad Software, Inc., CA, USA).

Results

Treatment adherence

Out of all 53 patients who were recommended OT by their physician, 45 patients (85%) performed OT, while 8 patients (15%) never performed OT (Table 2). At baseline, patients were instructed to perform OT consistently for at least 12 months. Only 36% of patients reported using OT consistently, while 64% had not (Figure 1). Furthermore, 51% of respondents stopped performing OT on their own without consulting their physician due to lack of self-perceived improvement. Conversely, 31% of respondents stopped performing OT against the physician's recommendation due to subjective improvement in olfactory function. Interestingly, there was a significant difference

Table 2. Treatment adherence questionnaire responses.

Variables	n (total)						
OT performed	53	n	%				
No		8	15.09				
Yes		45	84.91				
OT - Consistency	45	n	%				
Not consistent		29	64.44				
Consistent		16	35.56				
OT – Stopped due to lack of improvement	45	n	%				
No		22	48.89				
Yes		23	51.11				
OT – Stopped due to improvement	45	n	%				
No		31	68.89				
Yes		14	31.11				
OT - Time until discontinuation	30	n	Mean	SD	Min	Max	Median
in months		30	5.133	4.64	1	20	3
OT – Complaint on frequency	45	n	%				
No		27	60				
Yes		18	40				
OT - Forgetfulness	45	n	%				
All the time		11	24.44				
Frequently		4	8.89				
Occasionally		12	26.67				
Seldomly		10	22.22				
Never		8	17.78				

between aetiologies regarding the discontinuation of OT due to subjective improvement. While 33% and 47% of patients with post-traumatic and post-viral smell loss, respectively, ceased OT, only 11% of patients with idiopathic smell loss discontinued treatment based on the self-perceived gain in olfactory function (Fisher's exact test: p=0.033).

On average, patients who stopped treatment on their own performed OT for 5.1 (± 4.6) months (range: 1-20 months). There was no significant difference between the duration of use according to whether patients had discontinued OT based on improvement or non-improvement. However, patients who ceased OT due to improvement tended to perform it longer (6.3 vs. 4.4 months, Student t-test: p=0.266) (Figure 2).

Next, 40% of patients considered the recommended OT use twice a day as too often. In line with these findings, forgetfulness was high, with 24% and 9% of respondents stating that they forgot to perform OT "all the time" or "frequently", respectively. On the other hand, 27%, 22% and 18% of patients forgot OT "occasionally", "seldomly" and "never", respectively. Reported consistency of use was significantly associated with reported forgetfulness (Fisher's exact test: p<0.001), but unrelated to premature discontinuation of OT due to improvement or lack thereof (Supplementary Figure 2).

Olfactory function and olfactory training

Patients who performed OT had a significantly higher difference in their NRS score between the baseline and follow-up visit than patients who did not (1.5 vs. -0.8; p=0.015), while the TDI was not significantly affected by OT (Supplementary Figure 3A, B). There was no significant difference in TDI or NRS improvement according to OD aetiology in patients who performed OT (Figure 3A, B). Patients with a duration of OD at baseline of over two years showed significantly worse TDI outcomes (Supplementary Figure 4). In these patients, the proportion of idiopathic OD was significantly higher (Supplementary Table 3).

Olfactory improvement based on OT adherence

Objective improvement of olfactory function according to the TDI was significantly associated with discontinuing OT due to self-perceived lack of improvement (OR: 0.14 [CI: 0.03-0.74]; p=0.021). When adjusting for clinically relevant confounders, including age, gender, aetiology, duration of OD at baseline, and

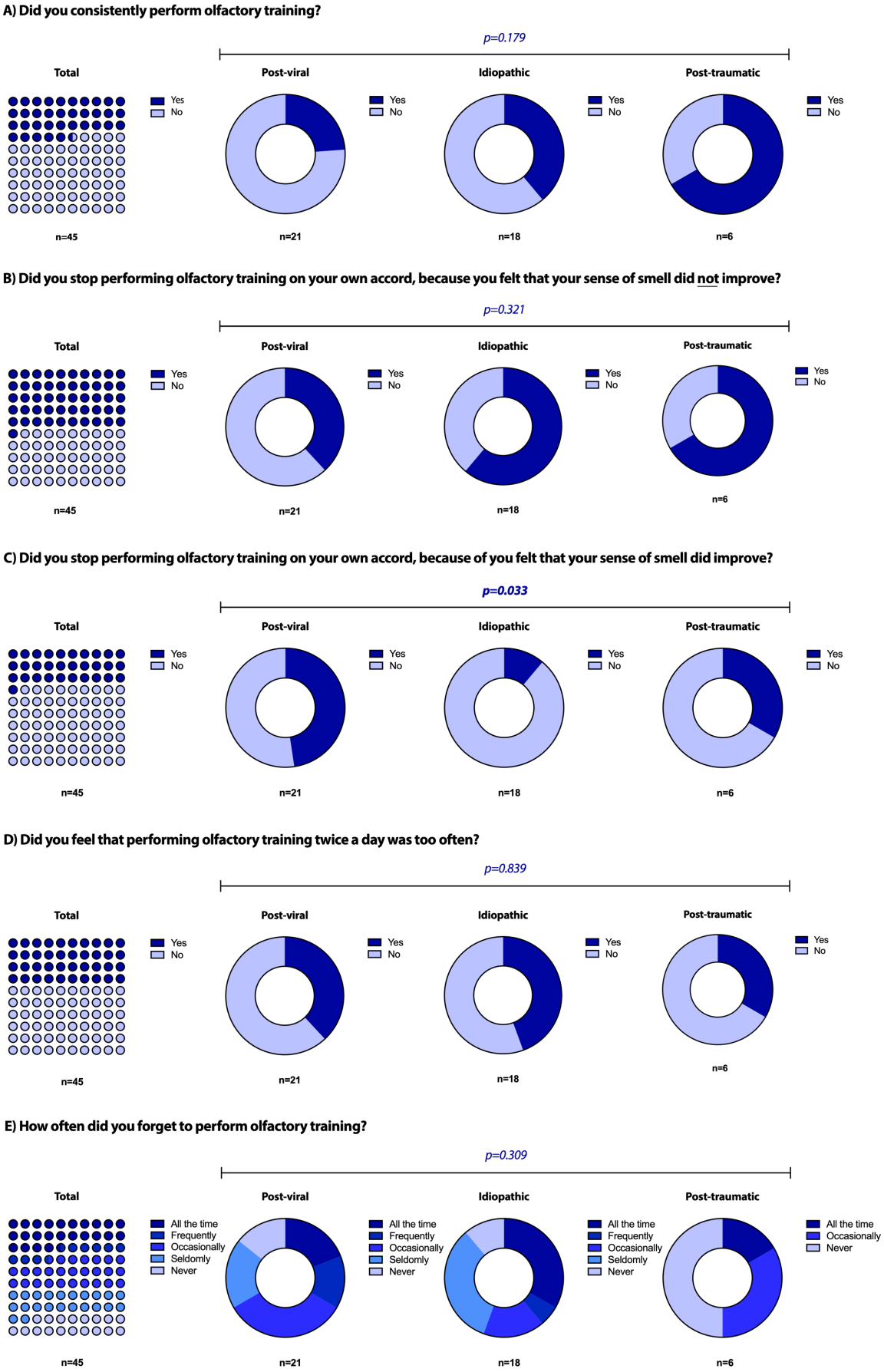

Figure 1. Treatment adherence questionnaire responses.

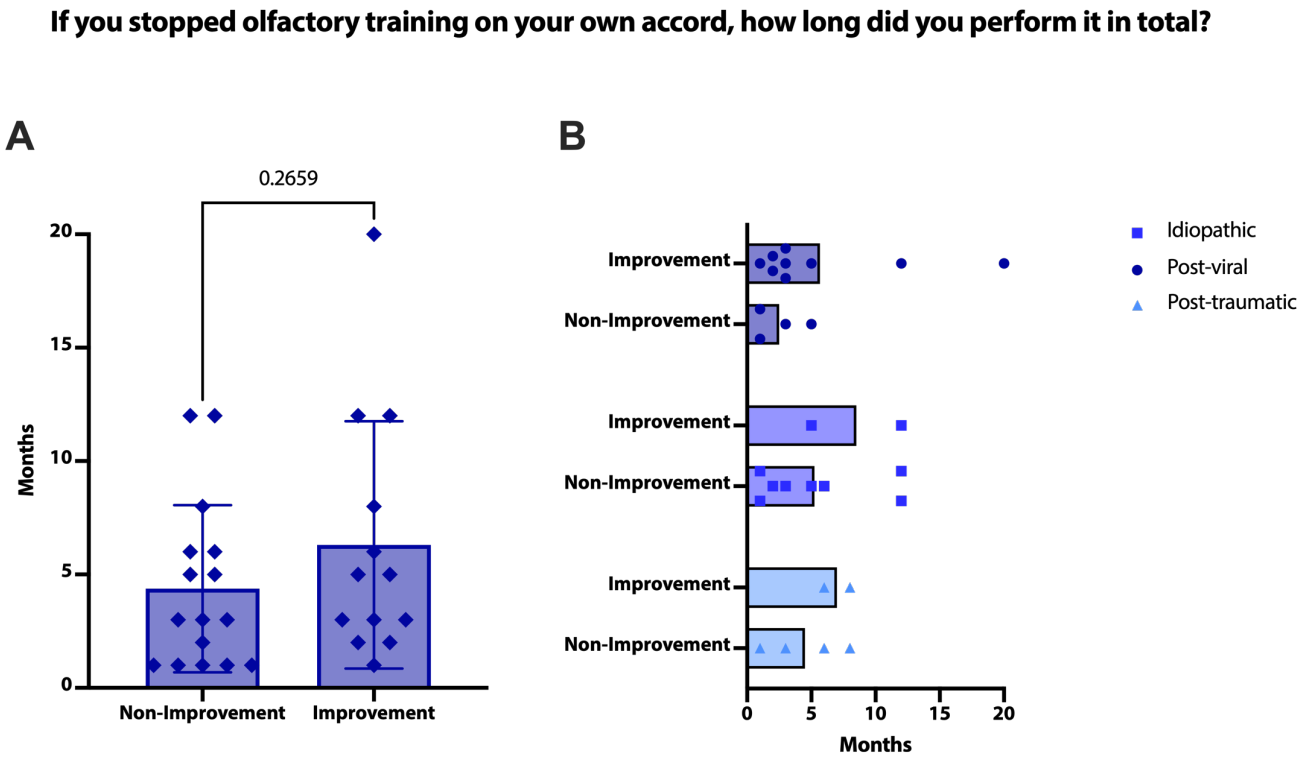

Figure 2. Months of olfactory training usage before discontinuation based on patients' perception of improvement or lack of improvement regarding their olfactory function in the entire cohort (A) and according to aetiology (B). Bars indicate the mean and standard deviation.

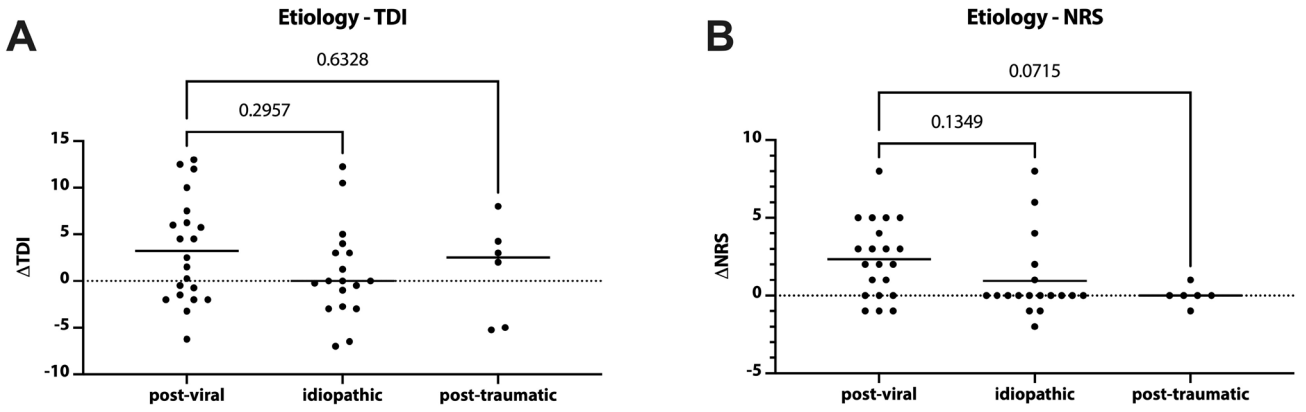

Figure 3. TDI (A) and NRS (B) differences between the baseline and follow-up time points regarding aetiology. Patients who never performed OT were excluded. The mean and individual data points are shown.

baseline TDI in multivariable analysis, this association remained significant (aOR: 0.11 [0.01-0.81]; p=0.030) (Supplementary Table 4).

Subjective improvement of olfactory function, according to the NRS, was significantly associated with post-traumatic (OR: 0.09 [0.01-0.87]; p=0.038) and idiopathic smell loss (OR: 0.15 [0.04-0.55]; p=0.004), baseline TDI (OR: 1.12 [1.01-1.25]; p=0.030) and discontinuation of OT based on both non-improvement (OR: 0.16 [0.05-0.60]; p=0.006) and improvement (OR: 7.70 [1.75-33.9]; p=0.007). In multivariable analysis, idiopathic smell loss (aOR: 0.07 [0.01-0.78]; p=0.031) and discontinuation of OT based on non-improvement (aOR: 0.13 [0.02-0.90]; p=0.038) remained significantly associated with subjective improvement of olfactory function. (Table 3)

In addition, all patients who did not perform OT experienced no subjective improvement of OT, while 46% of patients who did perform OT reported subjective improvement (Fisher's exact test: p=0.016).

Table 3. Binary logistic regression for NRS improvement.

		crude				adjusted				
Variables	**n**	**OR**	**CI low**	**CI up**	**p**	**n**	**aOR**	**CI low**	**CI up**	**P**
Age	53					45				
per unit increase		1.02	0.98	1.06	0.315		1.06	0.99	1.14	0.106
Gender	53					45				
male vs. female (ref)		1.95	0.64	5.95	0.241		11.52	0.91	145.91	0.059
Aetiology	53					45				
post-viral		ref					ref			
post-traumatic		0.09	0.01	0.87	**0.038**		0.09	0.01	1.42	0.087
idiopathic		0.15	0.04	0.55	**0.004**		0.07	0.01	0.78	**0.031**
Baseline TDI	53					45				
per unit increase		1.12	1.01	1.25	**0.03**		0.98	0.85	1.13	0.775
Duration of OD at baseline	53					45				
per 1 month increase		0.99	0.97	1	0.155		1.01	0.99	1.04	0.36
OT - Consistency	45					-				
consistent vs. not consistent (ref)		0.56	0.16	1.95	0.362		-	-	-	-
OT - Stopped due to lack of improvement	45					45				
yes vs. no (ref)		0.16	0.05	0.60	**0.006**		0.13	0.02	0.9	**0.038**
OT - Stopped due to improvement	45					45				
yes vs. no (ref)		7.70	1.75	33.90	**0.007**		8.89	0.95	83.03	0.055
OT – Time until discontinuation	30					-				
per 1 month increase		1.01	0.87	1.19	0.864		-	-	-	-
OT - Complaint on frequency	45					-				
yes vs. no (ref)		1.25	0.38	4.13	0.715		-	-	-	-
OT - Forgetfulness	45					-				
per unit increase		1.14	0.75	1.74	0.527		-	-	-	-
OT - Performed	-					-				
yes vs. no (ref)		omitted*	-	-	-		-	-	-	-

*"no" perfectly predicts lack of improvement

Discussion

OT is the current gold standard treatment for many aetiologies of OD [4]. However, the long-term course of OT requires at least three months, making adherence to OT an essential consideration for treatment success (26). In this study, we addressed the current lack of real-world data on OT adherence and investigated several dimensions using objective olfactory testing and subjective patient-reported outcome measures. We showed that 15% of patients did not perform OT at all despite their physician's recommendations, resulting in worse subjective olfactory function at follow-up without a significant impact on objective function. Additionally, almost two-thirds of patients who did perform OT reported inconsistent use, which was closely related to self-reported forgetfulness regarding OT. Half of the study population reported premature discontinuation of OT due to lack of improvement, significantly associated with worse objective and subjective improvement in olfactory function. Conversely, a third of patients discontinued OT prematurely due to self-perceived olfactory improvements, which was not significantly associated with olfactory outcome.

Hummel et al. first demonstrated the efficacy of OT in 2009 [7]. Damm et. al. then confirmed its effectiveness in treating post-infectious smell loss in the first randomized controlled study on OT in 2014 [27]. Since then, numerous studies and metanalyses have confirmed its effectiveness in treating OD of several aetiologies [8,28-31]. The effectiveness of OT for post-viral smell loss has been well established and appears to be the aetiology most likely to benefit from OT [6,8,29]. Nevertheless, OT is still a valid

treatment option for other causes of smell loss, including post-traumatic and idiopathic OD. Langdon et al. found a significant improvement in olfactory threshold in patients with smell loss related to traumatic brain injury after 12 weeks of OT [32]. However, after discontinuation of OT, the difference between the OT and the control group did not remain significant at the 24-week follow-up time-point. Konstantinidis et al. reported significant TDI improvements in post-traumatic OD cases performing OT with a negative correlation between olfactory function improvement and head trauma severity [33]. Pellegrino et al. added to these observations by proposing a top-down mechanism of post-traumatic olfactory rehabilitation after OT involving central neuroplasticity and increased attention to olfactory stimuli [34]. In post-viral smell loss, Kollndorfer et al. described OT-induced alterations in functional connectivity of central olfactory areas suggesting treatment-associated neuroplasticity [35]. Moreover, two other studies have reported improved olfactory function after OT in patients with idiopathic OD. These changes have been associated with increased olfactory bulb volume and regional gray matter volume [36,37].

Our study investigated several dimensions of adherence to OT. Incompliance and lack of treatment adherence is a pervasive issue in all disciplines of medicine and particularly affects long-term therapies. Current evidence suggests that approximately half of all patients receiving long-term pharmacotherapy do not take their medication as prescribed [38]. Barriers to adherence are plentiful and can be related to the patient, physician or health-care system [39]. The problem of treatment adherence in other chronic rhinological conditions, such as CRS and allergic rhinitis, has been well documented [15,40]. Long-term adherence rates to sublingual immunotherapy in allergy treatment are as low as 10% at the three-year mark [41]. However, research on adherence to OT remains sparse. In the present study, we showed that only 15% of patients showed complete incompliance. These rates are comparable, although slightly lower, to a recent study by Lechien et al., which showed a complete incompliance rate of 26% in COVID-19 patients who were prescribed a 12-week course of OT. Comparatively, partial incompliance was much more prevalent in our study, with almost two-thirds of patients reporting inconsistent use of OT. Philipps et al. reported comparably low consistent user rates for nasal saline irrigation of about 35% in CRS patients [15]. Saline irrigations are similar to OT in that they require considerably more effort than simply taking a pill or applying a nasal spray and cannot quickly alleviate symptoms, which likely impacts consistency of use.

Adding to the inconsistent use, about 50% of patients stopped OT without consulting their physician due to a lack of self-perceived improvement. An additional 30% discontinued OT prematurely due to subjective improvement of olfactory function. The average length of use in these patients was five months, with no significant difference in length of use between those who quit OT due to improvement and lack of improvement, respectively. However, patients without subjective improvement tended to stop treatment earlier across all three aetiologies. Although this trend will need to be confirmed in larger study populations, it first indicates that patients without any self-perceived olfactory improvement within the first two to three months may be particularly at risk for discontinuing OT. One prospective trial on OT adherence with 25 patients also reported declining OT adherence rates beyond three months, highlighting the challenge of convincing patients to adhere to longer OT regimens [21]. More importantly, we also showed that premature discontinuation of OT due to lack of improvement was significantly associated with worse objective and subjective olfactory outcomes. This observation is supported by a recent study in OT-treated COVID-19 patients, which showed an association of full training compliance with a higher probability of clinically relevant TDI improvements [42]. Finally, we showed that more than a third of patients considered performing OT twice a day too often and that two-thirds forgot to perform OT at least occasionally. Therefore, new strategies to improve convenience and combat forgetfulness are needed. First efforts to increase ease-of-use of OT have been made by Saatci et al., who demonstrated that using an OT ball improved adherence compared to classical OT [43]. Regarding the management of forgetfulness, online reminders could be a helpful tool in today's smartphone-driven society. Feng et al. showed a significant improvement in adherence to nasal corticosteroid sprays after functional endoscopic sinus surgery over three months by sending daily reminders via an online messaging service [44].

Our findings have several clinical implications. Given the high rate of patients discontinuing treatment on their own accord, patients should be advised at their first visit to perform OT as instructed, regardless of any subjective changes in the olfactory loss. Multiple studies have shown that objective and subjective olfactory functions are poorly correlated and can diverge considerably [45-48]. A patient's self-perceived change in smell is, therefore, not an adequate indicator of treatment success. Additionally, regular follow-up visits may help reinforce regular OT use, particularly for long-term use of up to a year, as habit-forming for complex treatment regimens poses one of the key challenges for adherence to therapy [49]. Moreover, the mechanism of action of OT may be more obscure compared to more familiar traditional medication in the form of pills or nasal sprays, which could affect willingness to perform OT [39]. As a result, some patients may require more explanation on how OT should work to improve acceptance towards a generally unfamiliar treatment modality. If such strategies fail to improve adherence, our findings further indicate that, although some studies showed longer regimens to result in improved olfactory recovery [13,50,51], they may not be feasible given the high proportion of patients who discontinued OT on their own accord after a median of

three months.

Finally, our results provide a basis for further research into the current implementation of olfactory training into clinical practice. Given the demonstrated low adherence rate to OT outside of clinical trials, it is reasonable to assume that reported OT benefits in the real world may also be related to spontaneous recovery in non-adherent patients. Further, it remains unclear how long after OD onset OT still provides sufficient effectiveness. Several prospective studies on OT have focused on enrolling patients with an OD duration at baseline of less than two years [27,32,50], while others have included wide ranges of disease duration [7,34,52]. Our data indicates that OT more than two years after OD onset may be less effective. Fleiner et al. reported similar findings, where patients with a baseline OD duration over two years showed a decreased mean TDI score at follow-up [53]. Altundag et al. reported an improved olfactory outcome in patients performing OT closer to post-infectious OD onset [54]. Admittedly, our observations may also be attributable to the higher proportion of idiopathic OD in study participants with an OD duration over two years since idiopathic OD generally correlates with a worse prognosis than post-infectious OD [6]. Furthermore, OD duration at baseline as a continuous variable did not significantly impact TDI and NRS outcome in our multivariable model, calling into question the rather arbitrary cut-off of two years encountered in the literature. Nevertheless, future studies with adequately powered control groups and an even distribution of aetiologies could provide valuable insights into whether training at all costs yields improved clinical outcomes or whether OT may be futile if performed too long after initial OD onset. It is important to elucidate further how long and up to what baseline OD duration patients should be recommended OT.

Although this was the first real-life study on treatment adherence for OT, including different causes, there were several limitations. First, the follow-up times varied between patients due to the cross-sectional study design. Therefore, the potential smell improvements in patients with shorter follow-ups of less than a year may have been underestimated. Second, our study investigated three common aetiologies of OD. Although we tested for differences between causes of smell loss, the post-traumatic group was considerably smaller compared to the post-viral and idiopathic groups. Therefore, our results may only hold limited applicability to post-traumatic OD patients. Third, we lacked an adequately powered control cohort of patients who did not perform OT since our study was focused on treatment adherence and the control cohort only consisted of patients who were completely incompliant, making it difficult to draw conclusions on OT effectiveness in our study population. Last, the long follow-up period potentially resulted in a recall bias in individuals with extended intervals between performing OT and answering the questionnaire. Nevertheless, our findings provide an important basis for future investigation into new strategies for improving treatment adherence to OT.

Conclusion

This study adds to the emerging literature on treatment adherence to OT and its implications for olfactory recovery. We showed that adherence to OT was low, with most patients discontinuing treatment prematurely based on subjective olfactory function, likely related to patients' satisfaction or disappointment with the self-perceived effectiveness of OT. Further investigation is needed to improve OT adherence and the real-world feasibility of longer OT regimens.

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Authorship contribution

MH: concept of study, analysis of results, write up of manuscript, critical review of all contents; JR: data collection, critical review of all contents; JK: data collection, critical review of all contents; CAM: concept of study, critical review of all contents; DTL: concept of study, collection of data, analysis of results, write up of manuscript, critical review of all contents.

Conflict of interest

The authors declare that there are no conflicts of interests regarding the publication of this paper.

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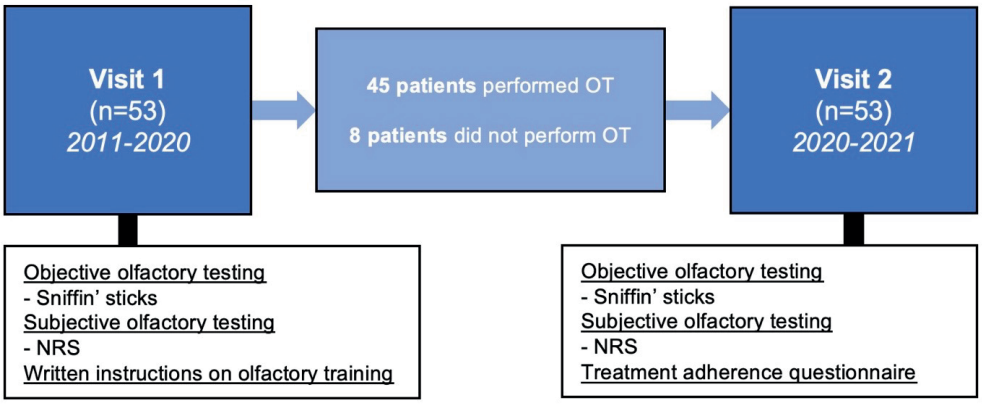
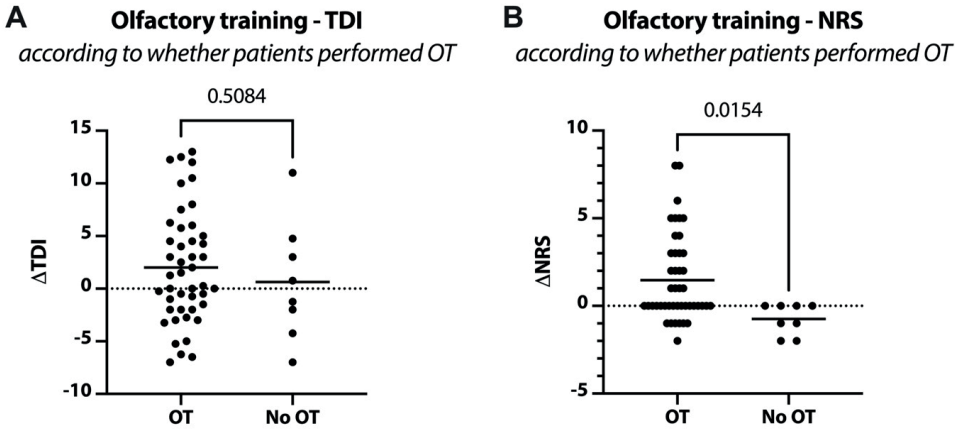
This manuscript contains online supplementary material

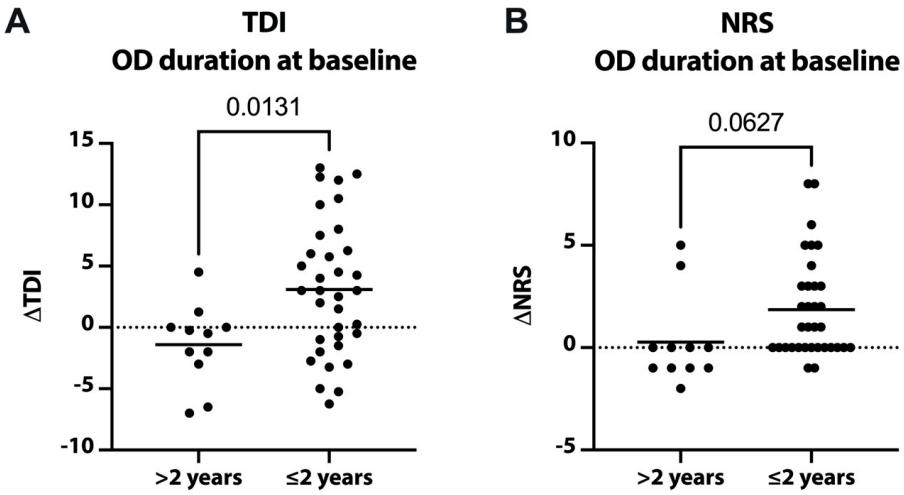
SUPPLEMENTARY MATERIAL



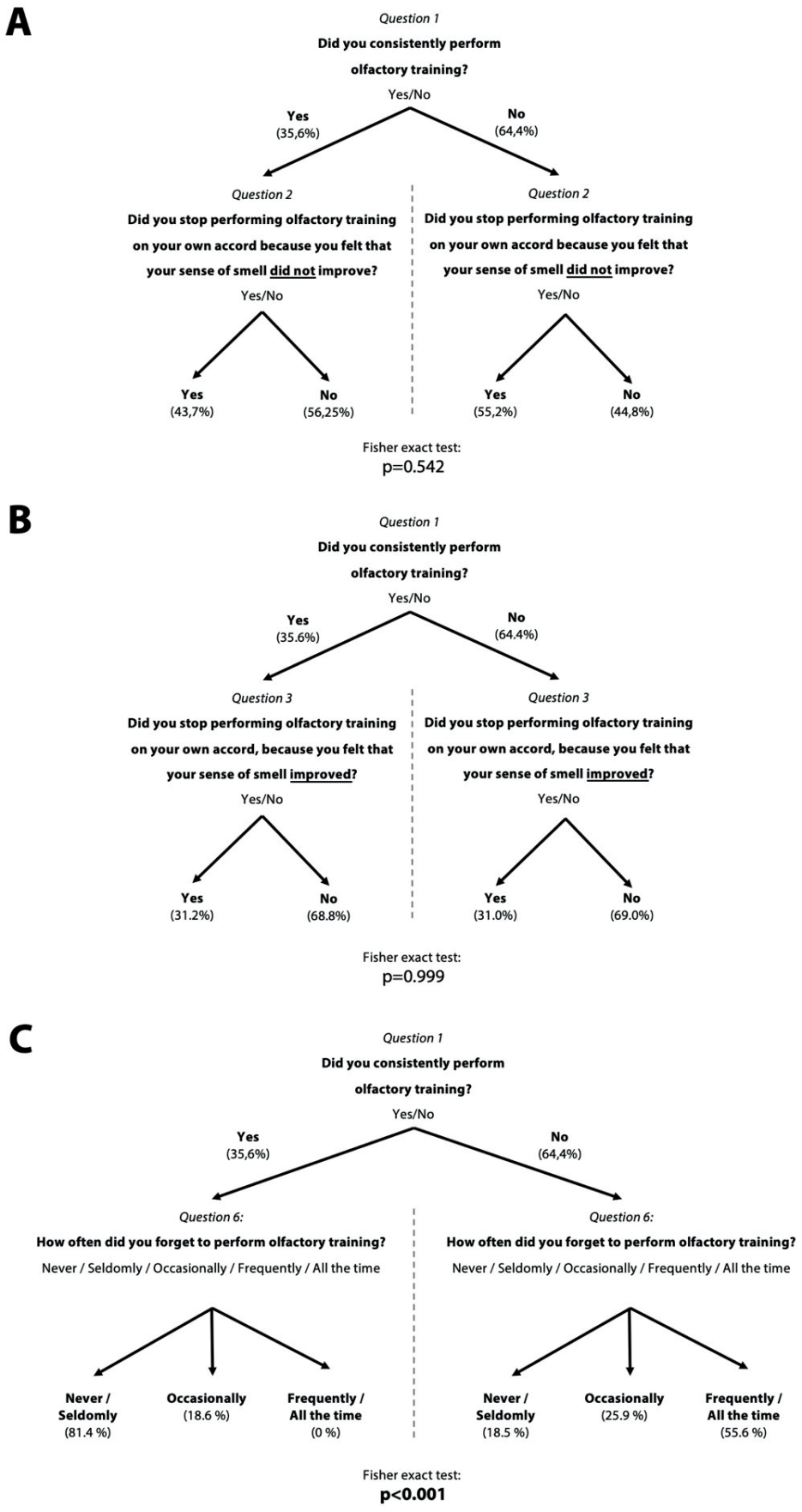
Supplementary Figure 1. Study design.



Supplementary Figure 3. TDI (A) and NRS (B) differences between the baseline and follow-up time points in patients who did perform OT compared to those who did not. The mean and individual data points are shown.



Supplementary Figure 4. TDI (A) and NRS (B) differences between the baseline and follow-up time points according to OD duration at baseline (>2 vs. ≤2 years).



Supplementary Figure 2. Association between patients' reported consistency, premature discontinuation of OT and forgetfulness.

Supplementary Table 1. Treatment adherence questionnaire (English translation).

Nr.	Question	Answer
1	Did you consistently perform olfactory training?	Yes/No
2	Did you stop performing olfactory training on your own accord because you felt that your sense of smell did not improve?	Yes/No
3	Did you stop performing olfactory training on your own accord, because you felt that your sense of smell improved?	Yes/No
4	If you stopped olfactory training on your own accord, how long did you perform it in total?	in months
5	The twice-a-day recommended use of olfactory training is relatively frequent. Some patients feel that twice a day is too often. Did you feel that performing olfactory training twice a day was too often?	Yes/No
6	How often did you forget to perform olfactory training?	Never/ Seldomly/ Occasionally/ Frequently/ All the time

Supplementary Table 2. Treatment adherence questionnaire (Original German version).

Nr.	Question	Answer
1	Haben Sie das Riechtraining bisher konsequent durchgeführt?	Ja/Nein
2	Haben Sie von sich aus das Riechtraining abgesetzt, weil Ihr Riechsinn sich nicht verbessert hat?	Ja/Nein
3	Haben Sie von sich aus das Riechtraining abgesetzt, weil Ihr Riechsinn sich verbessert hat?	Ja/Nein
4	Wenn JA bei Frage 3 oder 4, wieviel Monate haben Sie das Riechtraining durchgeführt?	in Monaten
5	Das täglich zweimalige Durchführen des Riechtrainings ist relativ häufig. Manche Patienten empfinden dies als zu oft. Haben Sie das täglich zweimalige Durchführen des Riechtrainings als zu oft empfunden?	Ja/Nein
6	Wie oft vergessen Sie, das Riechtraining durchzuführen?	Nie / Hin und wieder/ Manch-mal/ Gewöhnlich/ Immer

Supplementary Table 3. OD aetiologies according to OD duration at baseline (>2 vs. ≤2 years).

	Post-traumatic		Post-infectious		Idiopathic		Total		Fisher's exact
	n	%	n	%	n	%	n	%	p
OD duration at baseline									
≤2 years	6	17.65	18	52.94	10	29.41	34	75.55	
>2 years	0	0.00	3	27.27	8	72.73	11	24.45	**0.046**

Supplementary Table 4. Binary logistic regression for TDI improvement.

		crude					adjusted			
Variables	**n**	**OR**	**CI low**	**CI up**	**p**	**n**	**aOR**	**CI low**	**CI up**	**p**
Age	53					45				
per unit increase		0.99	0.95	1.03	0.669		0.97	0.92	1.03	0.34
Gender	53					45				
male vs. female (ref)		0.48	0.12	1.83	0.28		0.48	0.07	3.32	0.458
Aetiology	53					45				
post-viral		ref					ref			
post-traumatic		0.31	0.03	3.07	0.318		0.21	0.01	4.08	0.305
idiopathic		0.28	0.06	1.24	0.094		0.22	0.03	1.82	0.16
Baseline TDI	53					45				
per unit increase		1	0.9	1.11	0.991		0.9	0.75	1.07	0.231
Duration of OD at baseline	53					45				
per 1 month increase		0.99	0.97	1.01	0.334		0.99	0.97	1.01	0.461
OT - Consistency	45					-				
consistent vs. not consistent (ref)		0.61	0.14	2.71	0.511		-	-	-	-
OT - Stopped due to lack of improvement	45					45				
yes vs. no (ref)		0.14	0.03	0.74	**0.021**		0.11	0.01	0.81	**0.03**
OT - Stopped due to improvement	45					-				
yes vs. no (ref)		2.31	0.56	9.48	0.243		-	-	-	-
OT – Time until discontinuation	30					-				
per 1 month increase		1.13	0.95	1.34	0.166		-	-	-	-
OT - Complaint on frequency	45					-				
yes vs. no (ref)		1.35	0.34	5.32	0.671		-	-	-	-
OT - Forgetfulness	45					-				
per unit increase		0.94	0.58	1.52	0.806		-	-	-	-
OT - Performed	53					-				
yes vs. no (ref)		2.27	0.25	20.5	0.467		-	-	-	-