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Laryngopharyngeal Reflux: Effect of Antireflux PPI Therapy on Nasal Congestion and Olfaction

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ABSTRACT

Objective: *Laryngopharyngeal reflux (LPR) is responsible for many otorhinolaryngology manifestations. There is little evidence regarding the LPR impact on olfaction. No other study has investigated the efficacy of proton pump inhibitors (PPIs) on olfaction. We aimed to evaluate the effect of antireflux medication on olfaction and nasal patency in patients with LPR.*

Materials and methods: *Thirty patients with LPR were recruited. Nasal symptoms were self-evaluated with NOSE and SNOT-22 surveys, while a taste visual analogue scale (VAS) was used for gustation. Olfaction was evaluated with Sniffin' Sticks test and nasal patency with anterior rhinomanometry. After 12 weeks of oral PPIs, the procedure was re-applied and clinical outcomes were compared.*

Results: *Variables with statistically significant difference included the olfactory threshold (means 1,87/ SD 3,3/ t -3,11/ p 0,004) and the combined threshold-discrimination-identification (TDI) scores of Sniffin' Sticks test (means -2,61/ SD 5.26/ t -2.75/ p 0.01) and the self-assessment NOSE (p 0.009) and SNOT-22 (0.031) tests. However, no variable concerning nasal patency revealed statistically significant difference before and after treatment in the study group (p 0.677).*

Conclusions: *Oral PPIs treatment was associated with better olfactory threshold and TDI scores. These results raise the need for further studies, regarding the effect of antireflux medication on patients suffering from LPR who express nasal symptoms and olfaction disfunction.*

Keywords: gastroesophageal reflux, laryngopharyngeal reflux, nasal congestion and reflux, proton pump inhibitors and olfaction, olfaction disorders and reflux.

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INTRODUCTION

Laryngopharyngeal reflux (LPR) is called the reflux of gastric contents like gastric acid, pepsin, enzymes from pancreas and bile above the upper esophageal sphincter at the upper respiratory tract, while in gastroesophageal reflux gastric acid is limited to the esophagus. The exposure of the upper respiratory tract to gastric contents results in various otolaryngological manifestations (1, 2), namely chronic cough, laryngitis, hoarseness, globus pharyngeus, halitosis, chronic rhinosinusitis, postnasal drip, otitis media, olfaction and gustation impairment (3, 4).

The link between LPR and olfaction has gained an increased research interest among otolaryngologists due to the critical role of smell in people's overall quality of life. More specifically, olfaction along with trigeminal nerve pathways play a crucial role to the recognition of environmental hazards and contribute to pleasure perception, nutrition, mood and sexuality.

The objective of this study is to evaluate the effect of oral antireflux medication (PPIs) on olfaction and nasal patency in patients diagnosed with LPR. Very few studies investigating the impact of PPIs on nasal blockage/patency have been published until now, while the response of olfaction to pharmacological therapy has not been studied so far. The purpose of the present study is to investigate whether antireflux medication improves nasal patency and/or olfaction in patients with LPR.

MATERIALS AND METHODS

We conducted a prospective cohort clinical study at the Department of Otolaryngology of "Georgios Gennimatas" General Hospital of Thessaloniki, Greece, from April 2020 to March 2023.

The study protocol, informed consent and detailed intervention procedure were all submitted to the Ethics Committee for approval. Approval was also received from the Scientific Council of "Georgios Gennimatas" General Hospital of Thessaloniki and the Third Regional Health Directorate.

Patients with LPR symptoms were included in the study group and healthy individuals with no LPR symptoms were recruited for the control group.

Inclusion criteria

Laryngopharyngeal reflux was diagnosed using Belafsky criteria, including the Reflux Symptom Index (RSI) and Reflux Finding Signs (RFS) (5, 6).

The RSI questionnaire was filled in by the patient and the RFS one by the doctor after endoscopic assessment of the larynx.

Regarding RSI, patients were asked to complete a nine-item questionnaire assessing the severity of their symptoms. Each item was rated by a scale from 0 (no complaint) to five (severe symptoms). A score > 13 was indicative for LPR.

For RFS, participants underwent laryngoscopy by the same clinician and eight different signs were assessed. The score ranged from 0 (normal) to 26 (worst), with values higher than 7 being considered as indicative for LPR (5, 6).

If RFS>7 and RSI>13, we can accept that patients present LPR and are therefore eligible for the study group.

For the individuals of the control group, RFS≤7 and RSI≤13 was considered a necessary demand.

Exclusion criteria

The following exclusion criteria were applied: pediatric patients, acute or chronic rhinosinusitis, severe nasal septum deviation blocking completely one nostril, systemic diseases, neurodegenerative diseases, post-traumatic nasal or head injuries, all of which may cause some nasal dysfunction affecting olfactory function too. The control group included healthy individuals with no reflux symptoms (RFS≤7 and RSI≤13) and without a history of nasal disease.

Size effect

Since differences between two distinct parameters (smell/nasal congestion) were requested, we chose a large effect size index ($d = 0.8$), where the predicted sample size per cohort would be $N = 26$ people, at the level of significance $\alpha = 0.05$ and power index $\beta = 0.8$, according to Cohen (7). With this size index, the probability of a Type I and and Type II error was 5% and 20%, respectively, with a conservative assessment of the significance of the intervention in solving smell problems and nasal congestion (size index 0.5) (7).

Olfactory testing

For the evaluation of olfactory performance, Sniffin' Sticks test composed of 112 sticks was used to measure the threshold, discrimination and identification of odors.

The extended Sniffin' Sticks test procedure is a tool for the assessment of chemosensory function of the nose and it is based on distribution of smells with pen-like devices. It comprises three subtests of olfactory function: a test for olfactory threshold (n-butanol); a test for odor discrimination (16 pairs of odors, triple forced choice); and a test for odor identification (16 common odors, multiple forced choice among four written proposals).

In addition, patients were asked to fill in the NOSE and SNOT-22 questionnaires for self-evaluation of nasal symptoms, and a taste visual analogue scale (VAS) to assess their gustatory ability.

Finally, after the 12-week therapy with PPIs (lansoprazole 30 mg or esomeprazole trihydrate 40 mg), complete ENT examination was repeated, along with rhinomanometry, Sniffin' Sticks and self-evaluation by filling in the questionnaires.

Active anterior rhinomanometry

Rhinomanometry is a functional dynamic diagnostic tool for the evaluation of nasal resistance during nasal inspiration. It calculates intranasal pressure and airflow volume. Active anterior rhinomanometry is considered the gold standard for the assessment of the objective evaluation of total transnasal airflow resistance (8).

In the current study, anterior rhinomanometry, using Rhinomanometer Atmos 300, was applied for the investigation of nasal congestion before and after antireflux therapy in patients with diagnosed LPR. Anterior rhinomanometry was also used to assess nasal patency in the control group.

Statistical analysis

In our study, statistical analysis of outcomes was performed using IBM Statistical Package for Social Sciences (SPSS) 20 for Windows. The statistical comparison of the measured clinical variants was done 1) between the control group and the first clinical examination of the study group; and 2) between the first clinical examination and the reevaluation of the study group during a 12-week time. For the selection of the appropriate comparison test, the condition of normal distribution of the differences between the two measurements was examined. Paired samples t-test was used for normal distribution and Wilcoxon signed-ranks test for inverse Gaussian distribution. Pearson's Chi-squared t-test was employed for group comparisons in nominal variables and percentages. ❑

RESULTS

A control group of 30 healthy individuals and a study group of 30 patients with LPR were included in our study. All participants were assessed for their olfaction and nasal patency. Also, they self-assessed their nasal symptoms and taste sensation. The study group repeated the same protocol after a 12-week course of oral medication (Tables 1 and 4 summarise the values of the control and study groups before and after treatment).

Among the 30 subjects of the study group, there were 24 (80%) women with a mean age of 50.5 years [standard deviation (SD) 13.01 years] (age range 25–66 years) and six (20%) men with a mean age of 50.67 years (SD 6.92 years) (age range 40–60 years).

Among the 30 control group participants, there were 24 (80%) women with a mean age of 45.91 years (SD 11.52 years) (age range 22–63 years) and six (20%) men with mean age of 44.33 years (SD 9.61 years) (age range 28–56 years).

Comparison of the study group initial values and control group measurements

Tables 2 and 3 display comparisons between measurements of the control group and pre-

TABLE 1. Control group measurements

	Mean	SD	SE
RFS	3.10	.413	2.264
RSI	2.47	.459	2.515
Rtot	194.732	4.7	25.745
NOSE	9.67	1.932	10.581
SNOT	7.87	.965	5.283
ID	14.80	.162	.887
TH	11.066	.486	2.663
DISC	13.25	.384	2.104
TDI	39.116	.507	2.780
Taste VAS	9.00	.173	.947

SD: standard deviation;
SE: standard error

	Control group mean	Study group initial measurement mean	t	Df	Mean difference	p
RFS	3.1	11.5	11.213	58	8.400	<0.001
Rtot	**194.732**	**182.895**	**1.329**	**58**	**8.972**	**0.189**
SNOT	7.87	35.3	6.654	32.347	27.433	<0.001
TH	11.066	6.53	-6.206	58	-4.533	<0.001
TDI	39.116	31.9	-6.543	43.539	-7.216	<0.001

TABLE 2. Comparison of control and study groups before treatment measurements with the t-test

	Control group	Study group initial measurement	z	p
RSI	2.47	22.1	-6.672	<0.001
NOSE	9.67	38.67	-4.69	<0.001
ID	14.80	13.77	-2.754	0.006
DISC	13.25	11.60	-2.499	0.012
Taste VAS	9.00	7.17	-2.923	0.003

TABLE 3. Comparison of control and study groups before treatment measurements with Mann-Whitney test

TABLE 4. Values of the study group before and after treatment

		Mean	N	SD	SE
RFS	Before	11,5	30	3.42	0.62
	After	4	30	2.35	0.42
RSI	Before	22.1	30	7.93	1.44
	After	11.33	30	9.06	1.65
Rtot	Before	182.895	30	24.927	4.551
	After	185.760	30	26.546	4.846
ID	Before	13.77	30	1.61	0,29
	After	14.433	30	0.97	0,17
TH	Before	6.53	30	2,98	0,54
	After	8.41	30	2.73	0.49
DISC	Before	11.60	30	2.83	0.52
	After	11.66	30	2.35	0.43
TDI	Before	31.9	30	5.36	0.98
	After	34.54	30	4.68	0.85
NOSE	Before	38.67	30	24.63	4.49
	After	26.1	30	24.02	4.38
SNOT	Before	35.3	30	21.95	4.01
	After	25.8	30	21.28	3.88
Taste VAS	Before	7.17	30	2.75	0.5
	After	8.33	30	1.68	0.3

TABLE 5. Comparison of values obtained in the study group before and after antireflux therapy

Paired values t-test	Mean of difference	SD	t	p
RFS	7.5	3.73	11.013	**<0.001**
RSI	10.76	9.14	6.451	**<0.001**
Rtot	2.86	37.29	0.421	0.677
ID	-0.67	1.98	-1.83	0.077
TH	-1.87	3.3	-3.11	**0.004**
DISC	-0.06	2.95	-0.12	0.903
TDI	-2.61	5.26	-2.75	**0.01**
NOSE	12.56	24.5	2.81	**0.009**
Wilcoxon test	Mean of difference	SD	Z score	p
SNOT	-9.5		-2.152	**0.031**
Taste VAS	1.16		-1.913	0.056

treatment measurements of the study group. The appropriate tests for values with normal and non-normal distribution (t-test and Mann-Whitney test) were selected, respectively. The results showed statistically significant differences in all measured variables, except for total nasal resistance (p 0.189).

Comparison of measurements (values) pre- and post- treatment for the study group

We compared the RFS and RSI values for the study group, before and after three-month of antireflux medication. It is shown that mean values for both RFS and RSI after medication were reduced from 11.5 to 4 and from 22.1 to 11.33, respectively.

Pre- and post-treatment values were compared using the t-test for variable pairs and the

result showed statistically significant difference between pre- and post-treatment values ($p<0.001$) (Tables 4 and 5).

Comparison of nasal patency values

Active anterior rhinomanometry was used to evaluate participants' nasal patency before and after the three-month treatment with antireflux agents. Values before and after treatment are depicted in Figure 1 (Table 4).

The comparison revealed that treatment with PPIs did not affect nasal resistance. The mean total nasal resistance (Rtot) was 182.895 before treatment and 185.760 after treatment. Pre- and post-treatment values were compared using the t-test for variable pairs. Total resistance did not show statistically significant difference (p 0.677) (Table 5).

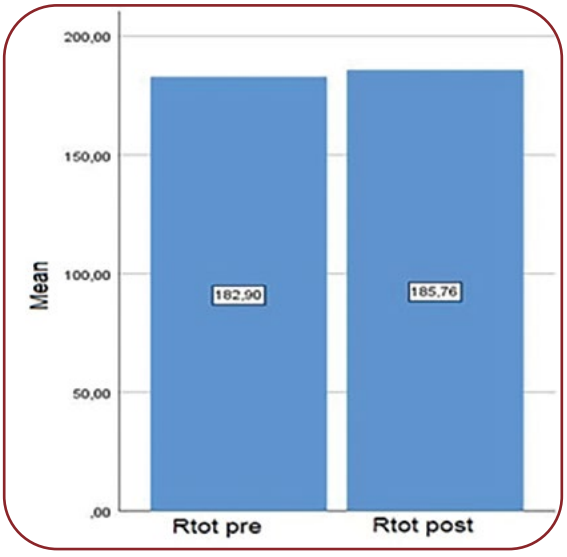

FIGURE 1. Comparison of nasal patency values before and after antireflux treatment

Comparison of Sniffin' Sticks test measurements

The Sniffin' sticks test procedure was used to assess olfaction before and after antireflux treatment. Identification, discrimination, threshold and TDI values are shown in Figure 2 and Table 4. The identification score was slightly improved from 13.77 to 14.433 (p 0.077) after treatment for LPR, while the discrimination score remained almost unchanged, from 11.60 to 11.66 (p 0.903). The threshold was improved from 6.53 to 8.41 (p 0.004) and TDI score also raised from 31.9 to 34.54 (p 0.01) (Table 5). It is worth mentioning that patients were fulfilling the exclusion criteria,

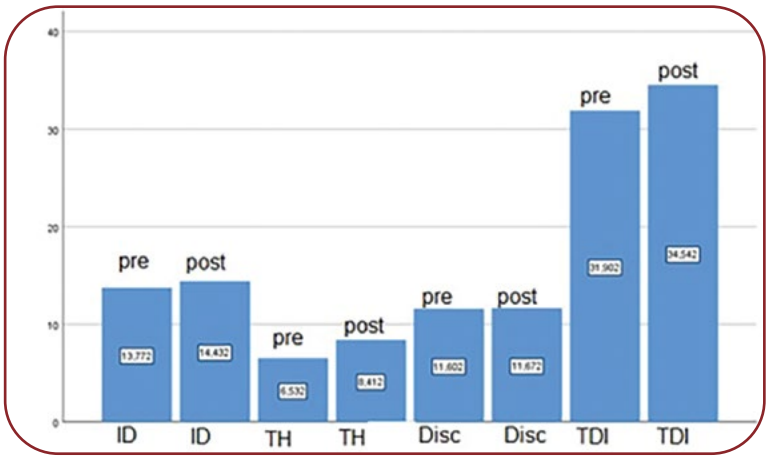

FIGURE 2. Comparison of results of measurements of Sniffin' sticks test before and after antireflux treatment

which potentially would affect the olfactory function. Also, they did not suffer any recent respiratory infection, including covid-19.

For comparison of pre- and post-antireflux treatment value, the paired samples t-test procedure was used. Values of threshold and TDI scores before and after antireflux medication showed statistically significant difference (Table 5, p 0.004 and p 0.01, respectively).

Comparison of self-assessment measurements of nasal symptoms and taste

To assess participants' perception of their nasal symptoms, we asked them to fill in the NOSE and the SNOT-22 questionnaires. Regarding taste, a VAS from 0 to 10 was used, with 0 standing for poor taste and 10 for excellent taste.

The values before and after antireflux therapy are listed in Figure 3.

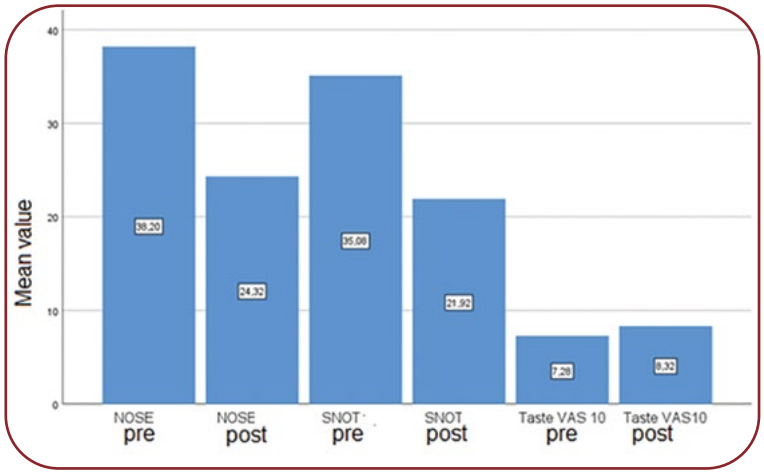

FIGURE 3. Comparison of measurements of self-assessment of nasal symptoms and taste before and after antireflux treatment

For the comparison of pre- and post-treatment values for the NOSE variable, the t-test for variable pairs was used (means 12.56 / SD 24.5 / t 2.81 / p 0.009). For the comparison of SNOT-22 and taste-VAS values, the Wilcoxon signed-ranks test was used (Table 5). For SNOT-22, the p value was 0.031, which revealed a significant improvement, though p 0.056 for taste VAS showed no statistically significant difference.

In summary, the differences between variable markers RFS ($p<0.001$) and RSI ($p<0.001$) were statistically significant, as expected after administration of PPIs, which implied a successful treatment. The variables of Sniffin tests, TH (p 0.004) and TDI (p 0.01), as well as the nasal symptom self-assessment variables NOSE (p 0.009) and SNOT (p 0.031) revealed statistically significant difference. The taste self-assessment variable approached the threshold of statistical significance (p 0.056). There was no statistically significant difference before and after intervention for nasal patency variables. ❑

DISCUSSION

It has been demonstrated that LPR affects olfactory function. This study aimed to investigate the impact of antireflux medication on olfaction in patients with LPR. The comparison of RFS/RSI markers between the healthy controls and LPR patients confirmed a statistically significant difference ($p<0.001$ for RSI and $p<0.001$ for RFS).

Our study concluded that patients with LPR, who took oral PPIs for three months, achieved a significant improvement of both the LPR symptoms (RSI) and endoscopic examination (RFS), which showed that the treatment was successful. According to the Sniffin' sticks test, they also showed significant improvement of their olfactory threshold (p 0.004) and total TDI score (p 0.01), which was a strong indication of reversible olfactory dysfunction due to reflux.

Individuals in the study group also had a significant decrease in nasal complaints according to both NOSE and SNOT-22, while their gustatory self-assessment reached the level of statistical significance.

Olfaction and laryngopharyngeal reflux

Normal olfaction depends on multiple interacting factors. The olfactory epithelium is crucial for olfaction as it is the receptive organ. Changes or injury in the olfactory area could potentially harm olfaction (9), as the application of a topical harmful agent leads to disturbance of the anatomy and physiology of the affected area. Consequently, preventing odorous compounds from reaching the olfactory area and stimulating the olfactory receptors decreases the olfactory capability (10). Recently, the connection between LPR and chronic rhinosinusitis as well as the impact of LPR on nasal mucosa has gained increasing attention (11). Laryngopharyngeal reflux has been demonstrated to directly affect nasal function and physiology and has been investigated by a few studies. However, the olfactory function has not been examined.

Laryngopharyngeal reflux seems to affect the olfactory function via two processes. According to the first one, chronic nasal inflammation is caused by increased nasal pepsin discharge, which is observed in reflux contents. Nasopharyngeal reflux is diagnosed in one third of patients with gastroesophageal reflux (GER), suggesting a direct toxic impact on the nasal mucosa (1, 12, 13).

The second mechanism supports the reflux stimulation of vagus nerve, which may lead to autonomous nervous system dysfunction. As a result, conductive nasal dysfunction develops because of severe edema of nasal mucosa and chronic rhinosinusitis (14).

Laryngopharyngeal reflux involves fewer episodes of reflux and reduced acid concentrations than GER but provokes severe damage to the oropharyngeal and laryngeal mucosa. Taste buds may be injured, resulting in dysgeusia, olfactory dysfunction and deterioration of mouth hygiene (15).

Mucosal exposure to reflux substances such as pepsin, bile salts and pancreatic enzymes has been associated with inflammation in both LPR and gastroesophageal reflux disease (GERD). Additional evidence suggests that pepsin can cause intracellular damage because cellular elements such as the Golgi complex and lysosomes have a low pH (5.0 and 4.0, respectively), which enables its activation. Similar inflammatory lesions to olfactory mucosa due to reflux could explain the impact on the olfactory threshold and TDI score that was recorded in the present study.

Furthermore, different causes of hyposmia are found to produce different patterns of olfac-

tory loss with respect to the specific subtests including threshold, discrimination and identification. Whitcroft *et al* concluded that patients with Parkinson disease performed relatively well in odor threshold testing but poorly in odor identification and discrimination compared with the other aetiology groups. Patients with postinfectious and posttraumatic hyposmia performed relatively well in both thresholds and discrimination but poorly in identification. Patients with posttraumatic hyposmia had generally reduced scores compared with the other groups. Odor identification impairment is believed to reflect damage in the brain regions that receive neuronal projections directly or indirectly from the olfactory bulb, including the piriform cortex, amygdala, hippocampal and entorhinal cortex and orbitofrontal cortex. Impairment in odor identification predicts cognitive decline (16).

Patients with infectious or other sinus diseases had a good performance on the odor recognition test and discrimination test but struggled with the threshold test (12). Conditions like paranasal disease, infection and inflammation can obstruct and cause toxic mucosal damage impacting the sensitivity to odors. This mechanism could potentially explain the effect of reflux content on the nasal mucosa in general and on the olfactory mucosa in particular.

Recently, our team performed a review analysis to evaluate current data regarding the impact of LPR on olfaction. Only seven studies were finally retrieved and included in the research (14). The above-mentioned studies performed no power analysis to estimate the number of cases needed for a valid conclusion. Most of the researchers did not mention restrictions.

Three out of seven studies used the recording of clinical findings (RFS index) and subjective symptoms (RSI) to evaluate the severity of LPR in their inclusion criteria. Emre Dinc *et al* used a double probe 24-hour pH monitoring, while Gunbey *et al* defined a six-month period with complaints, important for LPR diagnosis (17, 18). Beznig *et al* performed gastric biopsies to detect the presence of *H. pylori* and assumed that the pathogenic bacterium could reach nasal cavity through oronasal reflux (19, 20). The authors hypothesized that inflammatory mechanisms provoked by *H. pylori* infection could lead to olfactory dysfunction (21).

In our study, patients rated their nasal symptoms before and after treatment. The self-assessment variables of nasal symptoms NOSE and SNOT showed statistically significant differences before and after PPIs.

Therapy seems to be associated with improved subjective symptoms, which is not recorded to nasal patency measurement with anterior rhinomanometry. According to our results, patients showed a clinical improvement of their nasal symptoms when they received causal treatment (causative factor = reflux). Moreover, the subjective perception of the clinical improvement has a positive effect on their daily life.

Although Dagli *et al* reported a statistically significant difference concerning nasal patency before and after treatment for LPR, our research found no significant difference using anterior rhinomanometry (3). ❑

CONCLUSION

To our knowledge, this is the first study aimed at examining the nasal condition and olfaction after a three-month treatment with oral PPIs. A statistically significant improvement of olfactory threshold as well as of the composite score of olfactory function (TDI score) after a three-month systematic oral treatment with PPIs was recorded. The subjective nasal symptoms were also improved, affecting the patients' quality of life. These results raise the need for further studies on the effect of antireflux medication on LPR patients with nasal symptoms and olfaction disfunction. ❑

Conflicts of interest: none declared.

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Authors' contributions: VF and JH were involved in designing the study; VF has collected the data and wrote the initial draft with the help of NK. CS, IB and JH helped writing the manuscript. Finally, JH reviewed the final draft and advised on the scientific evidence-based support of the statistical analysis results. The first author (principal investigator) is prepared to take total responsibility for the integrity of the content of the manuscript.

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