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Clinical Profiles and Proton Pump Inhibitor Discontinuation Outcomes in Laryngopharyngeal Reflux Disease

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Abstract

Objective. To investigate the clinical presentation and weaning of patients with chronic proton pump inhibitor (PPI) therapy and laryngopharyngeal reflux disease (LPRD).

Study Design. Prospective controlled study.

Methods. Patients with LPRD symptoms despite ongoing PPI therapy were prospectively recruited from two centers. LPRD diagnosis required >1 pharyngeal reflux event on hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH) or reflux symptom score (RSS) > 13 with reflux sign assessment (RSA) > 14. A control group with primary LPRD diagnosis was established. All patients received diet modifications, lifestyle changes, and alginate/antacid therapy for 3 months while discontinuing PPIs. Clinical presentations and treatment responses were compared between groups using RSS and RSA. PPI weaning success rates and rebound effects were evaluated.

Results. Fifty-three patients with PPI therapy and 53 subjects with a primary LPRD diagnosis were consecutively recruited. PPIs were successfully discontinued in 66.0% of patients, with rebound effects occurring in 20.0% of weaned cases. Long-term PPI users (mean duration: 142.3 ± 153.9 months) exhibited significantly higher otolaryngological and respiratory symptoms than primary LPRD patients, while both groups showed comparable digestive symptoms. Only 5.7% of patients met criteria for long-term PPI therapy. Both groups demonstrated significant improvement in symptoms and signs following treatment. The PPI group showed greater reduction in reflux sign assessment scores ($P = .001$) compared to primary LPRD patients.

Conclusion. The chronic PPI consumption was not supported by clinical guidelines in most patients with LPRD. Most long-term PPI users with LPRD can successfully discontinue therapy when replaced with appropriate anti-reflux treatment alternatives.

Keywords

biomarkers, cough, diagnosis, digestive, enzymes, gastroesophageal, laryngopharyngeal, otolaryngology, otorhinolaryngology, proton pump inhibitor, rebound, reflux, weaning

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Laryngopharyngeal reflux disease (LPRD) is defined as a disease of the upper aerodigestive tract resulting from the direct and/or indirect effects of gastroduodenal content reflux, inducing morphological and/or neurological changes in the upper aerodigestive tract.[1] Proton pump inhibitors (PPIs) were considered the standard of care for a long time,[2] despite lack of demonstrated superiority over placebo[3] and moderate therapeutic response rates.[4] The limited effectiveness of PPIs relates to the weakly acid and alkaline nature of most LPRD cases on 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH),[5] supporting alginate and antacids as first-line treatment.[1] Due to PPI overconsumption, which may be related to systematic medication renewal from the general practitioner,[6] and their moderate effectiveness on LPRD symptoms, many patients present to otolaryngology offices with persistent LPRD symptoms despite chronic PPI use. Few studies have investigated the clinical presentation of these PPI-resistant LPRD patients, potential benefits of alternative treatments like alginates or antacids, and PPI weaning rates.[7]

This study aimed to investigate the clinical presentation and weaning of patients with LPRD symptoms persisting despite chronic PPI consumption. We hypothesize that these patients exhibit PPI-induced reduction in LPRD symptom severity, especially digestive symptoms, compared to those with primary LPRD diagnosis without ongoing treatment, and face high risk of rebound effects upon PPI discontinuation.

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Methods

Patients with LPRD symptoms and findings under ongoing PPI therapy were consecutively recruited from January 2022 to December 2024 at two medical centers (Dour Medical Center and CHU Saint-Pierre, Brussels, Belgium). According to the Dubai consensus[1] and European Clinical Practice Guidelines,[7] LPRD diagnosis required detection of more than one pharyngeal reflux event at 24-hour HEMII-pH monitoring or RSS > 13 with RSA > 14.[8,9] Since the study aimed to investigate PPI weaning and related rebound effects, HEMII-pH testing was not recommended for most PPI group patients due to the required 7-day PPI discontinuation before testing. Patients with conditions potentially causing LPRD-like symptoms underwent 24-hour HEMII-pH to confirm LPRD diagnosis. A control group comprised patients with new LPRD diagnosis based exclusively on 24-hour HEMII-pH without ongoing PPI therapy, and RSS > 13 and RSA > 14. In both groups, gastrointestinal endoscopy was performed in patients ≥60 years, those with GERD symptoms/findings, and individuals with history of GERD-related complications.[7]

Exclusion criteria for both groups included: excessive smoking (>5 cigarettes/day), alcohol dependence (>3 units/day), neurological or psychiatric illness, upper respiratory tract infections within the last month, current use of non-PPI anti-reflux treatments (antihistamines, alginates, antacids) or inhaled corticosteroids, previous neck surgery/trauma, vocal fold lesions, history of ear, nose, and throat radiotherapy, active seasonal allergies, chronic obstructive pulmonary disease, asthma, and other non-LPRD chronic cough etiologies.

The study protocol was approved by the local ethics committee (CHU Saint-Pierre board, protocol no. BE076201837630). Patients were invited to participate, and informed consent was obtained.

Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance-pH Monitoring

The catheter (Versaflex Z®; Digitrapper pH-Z Testing System; Medtronic) was introduced transnasally in the morning before breakfast. The catheter is composed of eight impedance segments and two pH electrodes, tailored to the patient's esophageal length. Six impedance segments were positioned along the esophagus zones (Z1 to Z6), positioned at 19, 17, 11, 9, 7, and 5 cm above the lower esophageal sphincter. Two sensors were positioned 1 and 2 cm above the cricopharyngeal sphincter in the hypopharynx. The two pH electrodes were placed 2 cm above the lower esophageal sphincter and 1 to 2 cm below the cricopharyngeal sphincter. The HEMII-pH tracing was analyzed through a standardized method.[1] A pharyngeal reflux event occurred when reflux reached the two pharyngeal sensors. According to the Dubai consensus,[1] LPRD was diagnosed as the occurrence of more than one acid, weakly acid, or alkaline pharyngeal reflux episode.

Clinical Evaluations

Patients of both groups prospectively completed the French versions of the RSS,[8] including the 22 most prevalent otolaryngological (n = 9), digestive (n = 9), and respiratory (n = 4) symptoms. The oral, laryngeal, and pharyngeal signs were evaluated by 2 blinded board-certified otolaryngologists (JRL and FB, a retired laryngologist) with the RSA.[9] Consistently with previous studies,[8,9] RSS > 13 and RSA > 14 is associated with a 89.1 to 94.5 sensitivity and 81.0 to 95.2 specificity.

Therapeutic Regimen and PPI Discontinuation

Treatment for both groups followed European guidelines for LPRD.[7] Patients received post-meal alginates (Gaviscon®; Reckitt Benckiser) or antacids (Riopan®, Magaldrate; Takeda) 3 times daily. PPIs were prescribed only for patients with GERD findings, including grade C/D esophagitis, esophageal stricture, Barrett metaplasia, or predominantly acid pharyngeal reflux events (HEMII-pH group). Selection between alginate and antacids depended on health insurance coverage. All patients followed a standardized anti-reflux dietary and lifestyle protocol.[7]

Reasons for long-term PPI consumption were documented in the PPI group. If the reason did not align with clinical GERD consensus,[10] PPI was progressively discontinued while implementing dietary recommendations and alginate/antacid treatment. PPI dose reduction involved decreasing to 15 mg (lansoprazole) or 20 mg (other molecules) daily for 1 week, followed by alternate-day dosing for another week. Patients were followed for rebound effects through a phone call by the first author of the paper in the days after the discontinuation of PPIs. Note that the semi-structured phone interview was based on a standardized list of rebound effects, for example, heartburn, throat pain/burning, cough, burping, epigastric pain, regurgitation, nausea, hiccups, sticky throat mucus, and clearing.

Statistical Analyses

Statistical analysis was conducted using the Statistical Package for the Social Sciences for Windows (SPSS version 29.0; IBM Corp.). Demographics and clinical evaluations were compared between PPI and primary LPRD groups with Mann-Whitney U test and Chi-square depending on the data characteristics. The pretreatment to posttreatment changes in clinical scores were assessed with the Wilcoxon rank test. A bivariate correlation was conducted across the clinical findings through a Spearman analysis. Spearman correlation coefficients were considered as low ($k < 0.40$), moderate ($k = 0.40$-0.60), and strong ($k > 0.60$). A significance level of $P < .05$ was used.

Results

Settings and Patients

Fifty-three patients completed pretreatment to posttreatment evaluations (30 females). The matched-gender control group comprised 53 patients with LPRD confirmed by 24-hour HEMII-pH (30 females) recruited from the same consultation. Patients with long-term PPI treatment were significantly older than those with primary LPRD (63.2 ± 12.9 vs 52.0 ± 15.0 years; $P = .001$). Body mass index of chronic PPI users was significantly higher than that of LPRD patients (**Table 1**). At inclusion, 2 (6.1%) PPI patients and 12 (22.6%) primary LPRD patients had GERD ($P = .001$) according to Lyon consensus.[10] The mean hypopharyngeal reflux event at the HEMII-pH was 32.0 ± 29.8. The mean number of acidic, weakly acidic, and alkaline pharyngeal events was 1.9 ± 3.4, 29.7 ± 29.0, and 0.4 ± 0.9, respectively.

PPI Consumption

Mean PPI therapy duration was 142.3 ± 153.9 months. In 34% of cases (n = 18), patients could not recall the PPI therapy indication. Medical record analysis revealed PPI prescriptions and renewals by family practitioners in 12 (22.6%) cases and gastroenterologists in 6 (11.3%) cases. In 18 (34%) cases, PPI therapy followed GI endoscopy reporting GERD findings (including esophagitis, Barrett metaplasia, or esophageal stricture) or other gastroesophageal conditions (eg, ulcers, gastritis, cancer history) (**Table 1**). In 17 (32.1%) cases, PPIs were prescribed for GERD symptoms without GI endoscopy recommendation. According to Montreal (2006)[11] and Lyon (2018)[10] consensus criteria, initial PPI therapy met consensus criteria in 18 cases (34%). Only three (5.7%) patients (one with esophageal cancer history, one with chronic gastric ulcer, and one with chronic Barrett metaplasia) met recommendations for long-term PPI therapy.

Clinical Presentation

Table 2 reports the clinical presentation comparison between patients with long-term PPI therapy history and those with primary LPRD diagnosis. Long-term PPI patients presented with significantly higher otolaryngological, respiratory, and total RSS compared to primary LPRD patients. This pattern did not extend to digestive symptoms, where both groups reported similar RSS item scores and subscores.

RSA comparison revealed significantly higher inflammatory oral scores in primary LPRD patients versus PPI patients, while the PPI group demonstrated higher laryngeal item finding scores compared to the control group (**Table 3**). Overall RSA was comparable between groups ($P = .055$).

Therapeutic Responses

Table 2 describes pretreatment to posttreatment RSS changes. Otolaryngological and respiratory symptoms improved significantly throughout treatment in both groups. Digestive item symptoms and RSS subscores remained unchanged in patients with long-term PPI therapy history (**Table 2**). Statistical comparison of pretreatment to posttreatment responses revealed comparable RSS reduction across groups, while RSA

Table 1. Demographics and Clinical Features of Patients

Outcomes	PPI patients N = 53	LPRD controls N = 53	*P* value
Age (mean, SD)	63.2 ± 12.9	52.0 ± 15.0	.001
Gender (N, SD)			
Females	30 (56.6)	30 (56.6)	NS
Males	23 (43.4)	23 (43.4)	
Body mass index (mean, SD)	26.6 ± 5.2	23.9 ± 5.6	.029
Duration of PPI therapy (mean, SD)	142.3 ± 153.9	-	
Reasons of long-term PPI therapy			
Esophagitis/Barrett metaplasia	10 (18.9)	-	
GERD symptoms without GI endoscopy	17 (32.1)	-	
Do not remember—Family practitioner prescription	12 (22.6)	-	
Do not remember—Gastroenterologist prescription	6 (11.3)	-	
Other GI findings (ulcers, gastritis, cancer history)	8 (15.1)	-	
GI endoscopy findings	33 (62.3)	26 (49.1)	
Esophagitis	9 (27.3)	11 (20.8)	NS
Hiatal hernia	7 (21.2)	8 (15.1)	NS
Lower esophageal sphincter insufficiency	11 (33.3)	10 (18.9)	NS
Gastritis	2 (6.1)	4 (7.5)	NS
Helicobacter pylori infection	0 (0.0)	0 (0.0)	NS

Abbreviations: GERD, gastroesophageal reflux disease; GI, gastrointestinal; m, mean; N, number; NS, nonsignificant; SD, standard deviation.

Table 2. Clinical Presentations of Patients

RSS items	PPI patients			LPRD controls			Intergroup
	Pre-treatment	Posttreatment	*P* value	Pretreatment	Posttreatment	*P* value	*P* value
Otolaryngological symptoms							
1. Voice disorder	8.3 ± 9.3	5.3 ± 8.3	NS	4.5 ± 6.4	2.7 ± 4.5	.034	.045
2. Throat pain	5.1 ± 6.6	3.3 ± 5.1	NS	5.5 ± 7.8	4.3 ± 6.0	NS	NS
3. Pain during swallowing time	5.2 ± 7.2	2.2 ± 4.8	.006	2.9 ± 4.9	1.5 ± 3.6	.021	NS
4. Dysphagia	8.5 ± 9.6	3.7 ± 7.4	.014	2.7 ± 5.2	1.2 ± 3.0	.012	.004
5. Throat clearing	12.7 ± 9.9	6.4 ± 8.3	.003	8.9 ± 8.5	6.5 ± 7.4	.007	NS
6. Globus sensation	11.5 ± 10.8	6.3 ± 8.9	.010	8.3 ± 8.5	6.1 ± 7.7	.039	NS
7. Excess throat mucus	13.0 ± 10.6	8.0 ± 9.5	.034	15.0 ± 23.3	7.6 ± 8.3	.001	NS
8. Ear pressure/pain	5.0 ± 7.5	3.9 ± 7.2	NS	3.6 ± 5.4	2.5 ± 4.6	.040	NS
9. Tongue burning	4.2 ± 7.8	3.1 ± 6.5	NS	3.3 ± 7.6	3.4 ± 6.5	NS	NS
Ear, nose and throat total score	73.3 ± 47.5	42.2 ± 39.7	.002	54.7 ± 41.2	34.6 ± 29.9	.001	.046
Digestive Symptoms							
1. Heartburn	7.2 ± 7.8	6.0 ± 7.9	NS	6.9 ± 7.4	4.1 ± 5.5	.006	NS
2. Regurgitations or burps	5.8 ± 7.8	4.8 ± 7.3	NS	6.2 ± 7.9	3.1 ± 5.0	.001	NS
3. Abdominal pain	4.9 ± 7.1	3.1 ± 5.6	NS	3.3 ± 5.9	2.1 ± 4.8	.039	NS
4. Diarrheas	3.4 ± 6.8	2.4 ± 6.5	NS	2.3 ± 5.7	0.6 ± 1.7	.003	NS
5. Constipation	6.1 ± 9.2	4.6 ± 9.1	NS	3.0 ± 5.6	1.9 ± 4.5	.027	NS
6. Indigestion	2.8 ± 6.2	1.6 ± 4.2	NS	2.1 ± 4.1	1.3 ± 3.2	NS	NS
7. Abdominal distension/flatus	5.9 ± 7.9	5.2 ± 7.7	NS	7.0 ± 8.2	4.3 ± 6.3	.003	NS
8. Halitosis	2.9 ± 5.3	2.3 ± 5.8	NS	4.3 ± 7.5	1.7 ± 4.1	.001	NS
9. Nausea	3.2 ± 6.6	2.0 ± 5.2	NS	1.7 ± 3.5	1.2 ± 2.5	NS	NS
Digestive total score	42.2 ± 40.1	32.0 ± 37.7	NS	36.6 ± 31.7	19.8 ± 21.8	.001	NS
Respiratory symptoms							
1. Cough after eating/lying down	11.2 ± 10.4	5.8 ± 8.2	.003	4.3 ± 7.3	2.3 ± 5.1	.012	.002
2. Cough	7.7 ± 9.1	4.3 ± 6.6	.007	5.1 ± 7.8	2.6 ± 5.4	.003	NS
3. Breathing difficulties	2.8 ± 5.5	1.9 ± 5.0	NS	2.1 ± 4.4	1.6 ± 4.3	NS	NS
4. Chest pain	8.8 ± 9.2	4.3 ± 6.8	.013	4.3 ± 6.2	1.9 ± 3.9	.002	.014
Respiratory total score	30.4 ± 22.6	16.3 ± 20.8	.001	15.8 ± 18.3	8.2 ± 12.7	.001	.001
RSS—Total score	146.0 ± 84.5	90.5 ± 89.1	.002	107.2 ± 70.1	62.6 ± 47.2	.001	.010

Abbreviations: LPRD, laryngopharyngeal reflux disease; NS, non-significant; PPI, proton pump inhibitors; RSS, reflux symptom score.

decrease was greater in the PPI group compared to the primary LPRD group ($P = .001$). Oral, laryngeal, and total RSA scores improved significantly from pre- to post-treatment in both groups without significant between-group differences (**Table 3**).

Weaning and Rebound Effects

Table 4 summarizes the clinical evaluation of PPI discontinuation. PPIs were successfully discontinued in 35 patients (66.0%) without rebound effects in 28/35 (80.0%) cases. PPIs were continued in 18 patients due to: indication for long-term therapy (n = 3) and significant rebound effects (n = 15) (**Table 4**). Primary symptoms associated with rebound included heartburn (n = 19), regurgitations (n = 14), groggy feeling (n = 14), and burping (n = 13) (**Table 4**). **Table 5** summarizes treatments throughout the study process. Among the 34 patients weaned from PPIs, 14 continued diet and lifestyle recommendations while 20 reported taking occasional alginate or antacids.

Association Analysis

The Spearman correlation analysis demonstrated a significantly negative association between the duration of PPI therapy and the baseline otolaryngological RSS ($r_s = -0.374$; $P = .019$). The patient age was significantly negatively associated with the digestive RSS ($r_s = -0.370$; $P = .020$), the RSS-QoL ($r_s = -0.353$; $P = .027$), and baseline RSA ($r_s = -0.329$; $P = .044$). The baseline RSS was predictor of the post-treatment RSS ($r_s = 0.369$; $P = .016$).

Discussion

The research of the past decades has increasingly demonstrated that laryngopharyngeal reflux disease (LPRD) and gastroesophageal reflux disease (GERD) are implicated in a wide variety of complaints, leading to a significant increase in patient visits to otolaryngologists, gastroenterologists, and internal medicine providers over the past two decades.[12] During this same period, LPRD medication use has increased by 233%, particularly PPIs.

Table 3. Finding Presentations of Patient Groups

Reflux sign assessment	PPI patients			LPRD controls			Intergroup
	Pretreatment	Posttreatment	*P* value	Pretreatment	Posttreatment	*P* value	*P* value
Oral cavity findings							
Anterior pillar erythema	3.7 ± 1.1	2.9 ± 1.8	.005	3.7 ± 1.1	3.5 ± 1.3	NS	NS
Uvula erythema ± edema	0.1 ± 0.1	0.3 ± 0.9	NS	0.9 ± 1.4	0.3 ± 0.9	NS	.001
Coated tongue	1.3 ± 1.0	1.1 ± 1.0	NS	1.4 ± 0.9	1.3 ± 1.0	NS	NS
Oral cavity subscore	5.0 ± 1.6	4.3 ± 2.5	.007	6.0 ± 2.1	5.1 ± 2.0	NS	.001
Pharyngeal findings							
Posterior oro- or hypopharyngeal wall erythema	0.2 ± 0.9	0.1 ± 0.1	NS	0.3 ± 1.1	0.1 ± 0.1	NS	NS
Posterior oro- or hypopharyngeal wall inflammatory granulations	0.1 ± 0.1	0.1 ± 0.1	NS	0.2 ± 0.8	0.2 ± 0.7	NS	NS
Tongue tonsil hypertrophy	3.1 ± 1.5	2.4 ± 1.6	.030	3.1 ± 1.4	2.6 ± 1.6	.021	NS
Contact between epiglotitis and tongue tonsils	3.0 ± 1.8	2.4 ± 2.0	NS	3.2 ± 1.6	2.8 ± 1.8	NS	NS
Pharyngeal sticky mucus	1.6 ± 2.0	0.6 ± 1.4	NS	2.1 ± 2.0	1.3 ± 1.9	NS	NS
Pharyngeal cavity subscore	7.9 ± 4.0	5.5 ± 4.0	.011	8.9 ± 3.6	6.9 ± 3.4	.015	NS
Laryngeal findings							
Ventricular band erythema ± edema	2.1 ± 1.4	0.9 ± 1.4	NS	2.6 ± 1.1	2.0 ± 1.4	NS	.001
Epiglottis redness ± edema	0.6 ± 0.9	0.2 ± 0.6	.001	1.2 ± 1.0	0.4 ± 0.8	.007	.001
Commissure posterior/arytenoid erythema	2.3 ± 2.2	1.4 ± 1.9	.022	3.1 ± 1.9	2.0 ± 2.1	.005	NS
Inter-arytenoid granulatory tissue	0.2 ± 0.5	0.1 ± 0.5	NS	0.1 ± 0.4	0.1 ± 0.4	NS	NS
Posterior commissure hypertrophy	4.1 ± 1.9	2.0 ± 2.5	.001	3.8 ± 2.2	2.7 ± 2.5	NS	NS
Retro-cricoid erythema	0.1 ± 0.1	0.1 ± 0.1	NS	0.5 ± 1.2	0.2 ± 0.9	NS	.015
Retro-cricoid edema	3.3 ± 1.5	0.9 ± 1.7	.001	2.3 ± 2.0	2.3 ± 2.0	NS	.022
Laryngeal sticky mucus deposit	0.5 ± 1.2	0.4 ± 1.1	NS	1.3 ± 1.6	0.9 ± 1.4	NS	.014
Laryngeal subscore	13.0 ± 4.5	6.3 ± 5.4	.001	14.8 ± 4.4	10.6 ± 4.7	.001	NS
RSA total	25.9 ± 7.8	16.1 ± 9.1	.001	29.7 ± 7.1	22.5 ± 7.4	.001	.055*

Abbreviations: NS, nonsignificant; RSA, reflux sign assessment.

In 2013, Francis et al demonstrated that the national US cost burden of diagnosing and treating LPRD could be 5.6 times the cost of treating GERD, with total expenditure estimated at more than $50 billion annually.[13] More recently, a European study suggested that both the lack of awareness about LPRD and ineffective PPI prescription practices are associated with increased public healthcare system costs.[14] In the country where the present study has been conducted (Belgium), the annual cost of PPI use was estimated to 109,460,799 euros, with a 1.63% increase from 2021 to 2023.[15] Thus, to date, chronic PPI consumption for GERD and LPRD represents a significant cost burden in both the United States and Europe.[13,14]

The findings of the present study suggest that a substantial number of patients with LPRD symptoms and findings who chronically use PPIs do not meet the criteria for long-term PPI therapy. In most cases, PPIs were prescribed long ago for gastrointestinal findings or GERD-related symptoms and were never discontinued. This observation corroborates those of Gendre et al who investigated the indication and long-term prescription of PPIs in France.[16] The authors reported that the prevalent patient population increased year after year, reaching 167,751 patients in 2020, with an increasing rate of 4.2% to 4.4% between 2017 and 2020. Similar to the present study, the majority (87.1%) of treatment initiations were performed by general practitioners with continuous prescription renewal.[16] Recent observational studies conducted in various French hospitals revealed that 30% to 60% of hospitalized patients were on PPIs at admission, and that of these prescriptions, only 16% to 40% complied with Marketing Authorization indications.[17] In 20% to 50% of cases, the indication for the treatment was not known and was initiated prior to hospitalization.[18] Our observation that 5.7% of patients did not meet the criteria for long-term use of PPIs corroborates these literature findings.

In clinical practice, many patients consult in otolaryngology for LPRD symptoms and findings despite chronic use of PPIs. From a therapeutic standpoint, this population is challenging and poorly investigated in the otolaryngology literature. Our initial hypothesis suggested that the ongoing use of PPIs reduced the severity

Table 4. Posttreatment Consequences of Proton Pump Inhibitor Discontinuation

	Patients (N, %)
Outcomes	n = 53
1. PPI discontinuation without rebound effects	24 (45.3)
2. PPI discontinuation without rebound effect and occasional alginates/antacids	4 (7.5)
3. PPI discontinuation with a controlled rebound effect	7 (13.2)
4. PPI continuation because rebound effects	15 (28.3)
5. PPI continuation because indication of long-term treatment	3 (5.7)
Symptoms of rebound effect	n = 20[a]
Heartburn	19 (95.0)
Cough	7 (35.0)
Burping	13 (65.0)
Epigastric pain	6 (30.0)
Feeling of being groggy	14 (70.0)
Regurgitation	14 (70.0)
Nausea	6 (30.0)
Hiccups	10 (50.0)
Throat clearing	1 (5.0)

[a]Two patients did not identify the key symptoms of rebound effects.
Abbreviation: N, number.

of some LPRD- and GERD-related symptoms and findings, leading to patients exhibiting lower RSS at baseline. However, the results of the present study demonstrated the opposite, as patients under PPIs with clinical LPRD reported higher RSS than those diagnosed with primary LPRD. To the best of our knowledge, there is no similar study in the otolaryngology literature. Several explanations can be provided.

First, the ineffectiveness of PPIs in some LPRD patients is consistent with recent literature demonstrating a lack of superiority of PPIs over placebo,[3] and the alkaline pattern of most LPRD cases.[5] This population of LPRD patients consists of subjects with weakly acidic and alkaline pharyngeal reflux events, and mucosa injury related to enzymes activated in alkaline pH (eg, elastase, trypsin, bile salts).[19] The role of these enzymes was supported in a recent study demonstrating that elastase is potentially associated with laryngopharyngeal mucosa injuries and related chronic cough.[20] Second, the population under PPIs with LPRD symptoms and findings could consist of subjects with severe and recalcitrant LPRD, which was highlighted by high RSS. Three clinical categories of LPRD patients have been recently identified, including patients with acute, recurrent, and chronic LPRD.[21] The proportion of chronic LPRD could be higher in individuals with ineffective PPI therapy compared to those presenting with primary LPRD (control group).

Regardless of the mechanisms underlying the higher severity of symptoms in patients with chronic use of PPIs, the discontinuation of PPIs and the control of symptoms with lifestyle changes (stress, anxiety reduction), diet, and occasional alginate or antacids was possible in 66% of patients. This observation supports the recent literature highlighting that PPI prescriptions might be unnecessary if acid reflux is not the cause of patient complaints.[22] Although long-term follow-up is still needed to draw valid conclusions, these preliminary observations could encourage practitioners to reduce the long-term prescription of PPIs, which can decrease PPI adverse events and the cost burden for healthcare systems. While PPIs are safe in the short term, emerging evidence shows risks associated with long-term use, including osteoporosis, lung and digestive infections, or malabsorption.[23,24] One of the adverse effects of long-term PPI use is rebound acid hypersecretion, which occurred in 28.3% of our patients. The mean prevalence of rebound effect is around 40-50% in the literature.[25] Our lower incidence could be attributed to the prescription of alginate and antacids at the time of PPI discontinuation. However, the risk of rebound effects and the related inability to discontinue PPIs need to be considered by otolaryngologists in the deprescription of PPIs.

The low number of patients is the primary limitation of this study. This investigation was a pilot study evaluating the clinical presentation differences between patients consulting for primary, untreated laryngopharyngeal reflux disease (LPRD) versus those with LPRD under PPIs, and the ability to discontinue PPIs. Our preliminary results encourage the continuation of the study, including a higher number of patients.

The lack of systematic use of hypopharyngeal-esophageal multichannel intraluminal impedance pH (HEMII-pH) testing in the PPI group, particularly after the treatment course, can be considered a potential limitation. However, we did not indicate HEMII-pH because this examination required the discontinuation of PPIs for 7 days,[1,7] which could influence the conduct of the study (observation of PPI-discontinuation rebound effect for patients adhering to a diet and alginate/antacid therapy). The exclusion criteria and the use of Reflux Symptom Score (RSS) > 13[8] and Reflux Sign Assessment (RSA) > 14[9] can limit the risk of including patients without LPRD. Further studies with higher number of patients and long-term findings of discontinuation of PPI should evaluate the potential benefits in terms of side effects associated with PPI use, including osteoporosis, cardiac events, or malabsorption of minerals and vitamins, and cost burden for healthcare systems.

Conclusion

The chronic PPI consumption was not supported by clinical guidelines in most patients with LPRD and GERD. Most long-term PPI users with LPRD can successfully discontinue therapy when replaced with appropriate anti-reflux treatment alternatives. Future

Table 5. Pre- to Posttreatment Changes in Symptoms and Findings in Patients Without Chronic Cough

Baseline treatments	N (%)	Weaning treatment (mo 0 to 3 mo)	N (%)	Long-term treatment	N (%)
Pantoprazole 20 mg	12 (23.1)	Alginate	14 (26.9)	PPI discontinuation group	
Pantoprazole 40 mg	16 (30.8)	Magaldrate	4 (7.7)	Alginate (occasional use)	12 (23.1)
Pantoprazole 60 mg	1 (1.9)	Aluminum/Magnesium hydroxide	1 (1.9)	Magaldrate (occasional use)	7 (13.5)
Pantoprazole 80 mg	1 (1.9)	Progressive PPI reduction		Aluminum/Magnesium hydroxide	1 (1.9)
Esomeprazole 20 mg	3 (5.8)	Pantoprazole 20 mg + Alginate (3/d)	12 (23.1)	Diet	14 (26.9)
Esomeprazole 40 mg	5 (9.6)	Pantoprazole 20 mg + Magaldrate (3/d)	4 (7.7)	PPI continuation group	
Omeprazole 20 mg	4 (7.7)	Pantoprazole 40 mg + Alginate (3/d)	4 (7.7)	Pantoprazole 20 mg + Alginate (occasional use)	2 (3.8)
Omeprazole 40 mg	4 (7.7)	Pantoprazole 40 mg + Magaldrate (3/d)	1 (1.9)	Pantoprazole 20 mg + Magaldrate (occasional use)	3 (5.8)
Rabeprazole 20 mg	1 (1.9)	Omeprazole 20 mg + Alginate (3/d)	4 (7.7)	Pantoprazole 20 mg	3 (5.8)
Pantoprazole (no dose reported by patient)	2 (3.8)	Omeprazole 20 mg + Magaldrate (3/d)	2 (3.8)	Pantoprazole 40 mg + Alginate (occasional use)	3 (5.8)
Esomeprazole (no dose reported by patient)	1 (1.9)	Omeprazole 40 mg + Alginate (3/d)	1 (1.9)	Omeprazole 20 mg + Magaldrate (occasional use)	1 (1.9)
Omeprazole (no dose reported by patient)	1 (1.9)	Esomeprazole 20 mg + Alginate (3/d)	3 (5.8)	Omeprazole 20 mg	1 (1.9)
Pantoprazole 20 mg + Esomeprazole 20 mg	1 (1.9)	Esomeprazole 20 mg + Magaldrate (3/d)	1 (1.9)	Omeprazole 40 mg + Alginate (occasional use)	1 (1.9)
		Esomeprazole 40 mg + Alginate (3/d)	1 (1.9)	Omeprazole 40 mg + Magaldrate (occasional use)	1 (1.9)
				Esomeprazole 20 mg + Alginate (occasional use)	1 (1.9)
				Esomeprazole 20 mg + Magaldrate (occasional use)	1 (1.9)
				Esomeprazole 20 mg	1 (1.9)

Abbreviations: mo, month; N, number; PPI, proton pump inhibitors.

large-cohort studies are needed to evaluate the long-term findings of discontinuation of PPI, and the potential benefit in term of adverse events and cost for healthcare system.

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Author Contributions

Lea Geoffroy, data interpretation, revising the manuscript for important intellectual content; final approval of the version to be published, final approval, and accountability for the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. **Jerome R. Lechien**, data interpretation, revising the manuscript for important intellectual content; final approval of the version to be published, final approval, and accountability for the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures

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