Pharmacological and Biological Relevance in the Medical Treatment of Laryngopharyngeal Reflux: A State-of-the-Art Review

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Abstract: The laryngopharyngeal reflux disease (LPRD) treatment remains controversial due to the poor effectiveness of proton pump inhibitors (PPIs). In this paper, the author reviewed the current primary treatments used in clinical studies for managing LPRD and discussed the pharmacological, biological, and physiological properties of medication for providing clinical relevance for otolaryngological practice. A comprehensive review of the PubMed, Cochrane Library, and Scopus literature was conducted to document and analyze the medical treatments of LPRD in the largest case series published in the past 20 years. Fifty-five studies met the inclusion criteria, revealing that 67 different therapeutic regimens were used in the LPRD studies in the past 20 years with nine different therapeutic durations. PPIs have been used as a single therapy in 70.1% of cases. PPIs were combined with another drug in 23.9% of cases. Alginates and antacids were used as single therapy or in association with other drugs in 10.5% and 3.0% of cases, respectively. There was an important variability of molecules, doses, and regimens. There is an important gap between current therapeutic practice and the recent advancements in the pathophysiology of LPRD. The pharmacological and physiological findings of this review can reasonably support the notion that alternative gastroesophageal reflux disease therapies (alginate, antacids) could take a significant place in the treatment of primary or recalcitrant LPRD. Future studies are needed to confirm the stability of the LPRD profile at the hypopharyngeal-esophageal multichannel intraluminal impedance-pH and the role of digestive enzymes in the development of upper aerodigestive tract mucosa inflammation and symptoms.

Key Words: Laryngopharyngeal—Reflux—Gastroesophageal—Medication—Treatment—Therapy— Otolaryngology—Head neck surgery—Laryngology..

INTRODUCTION

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] LPRD has long time been considered a condition with extra-esophageal manifestations of gastroesophageal reflux disease (GERD). However, LPRD and GERD are currently considered distinct diseases that share some common pathophysiological mechanisms.[1,2] The reflux disease is weakly acid and alkaline in LPRD, and the mucosa toxicity can be related to a myriad of enzymes (pepsin, bile acids, and possibly trypsin), which are activated in acid, weakly acid, or alkaline pH environment.[3,4] The past consideration of LPRD as an extra-esophageal reflux disease led practitioners to primarily treat LPRD similarly to GERD with proton pump inhibitors (PPIs) or, in case of recurrence, fundoplicature.[5,6] However, the superiority of PPIs over placebo has never been demonstrated in LPRD,[7] while the effectiveness rate of PPI therapy ranges from 17% to 87% of LPRD cases.[8] The poor therapeutic responses to PPI therapy led some authors to conduct controlled studies investigating the effectiveness of alternative medications, including alginate, antacids, or prokinetics, in the LPRD treatment. Thus, the number of controlled studies comparing several medications in LPRD particularly increased in the past few years.[9–12] Some recent studies supported that alginate or antacid medications could be as effective as PPIs and should be considered as primary therapeutic options or alternative treatment in case of PPI resistance.[9–13] Despite increasing evidence about the potential therapeutic roles of alginate and antacids for treating LPRD, a large majority of practitioners continue to prescribe PPIs as the primary empirical treatment,[5,14] while the common trend is to increase the PPI doses in case of therapeutic resistance.[14,15]

The primary objective of this state-of-the-art review was to review the primary treatments used for treating LPRD in the largest clinical studies published in the past 20 years. From the findings of the initial research, the pharmacological and physiological properties of LPRD medication were discussed for providing clinical relevance for otolaryngological practice.

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METHODS

The author of the paper (J.R.L.) and a librarian conducted an electronic search through PubMed, Cochrane Library, and Scopus to identify peer-reviewed studies reporting medical treatments of LPRD. According to the high number of clinical trials, case series, or prospective uncontrolled studies, the authors selected the largest cohort studies, including more than 50 patients with suspected or confirmed LPRD. The patients were considered as LPRD patients if the diagnosis was based on the detection of > 1 pharyngeal reflux event at the 24-hour ambulatory hypopharyngeal-esophageal multichannel intraluminal impedance-pH (HEMII-pH) monitoring, pharyngeal pH monitoring, or dual- or triple-probe pH monitoring.[1] Patients with laryngopharyngeal symptoms or findings and GERD at the single-probe pH metry or multichannel intraluminal impedance-pH monitoring (MII-pH) were considered as suspected LPRD patients.[1] The following search terms were used as keywords: "reflux," "laryngitis," "laryngopharyngeal," "gastroesophageal," "extra-esophageal," "PPIs," "alginate," "antacid," "magaldrate," "prokinetics," "treatment," and "therapy." The authors analyzed the full texts of the selected papers. The author and library assistant considered studies if they had database abstracts, available full texts, or titles containing the search terms. Studies were published in English, Spanish, and French language. Only clinical prospective/retrospective uncontrolled/controlled studies reporting data of more than 50 patients were considered for this initial search. The author and library assistant examined the reference lists of meta-analyses, state-of-the-art, or systematic reviews for additional pertinent studies. Case reports and publications focusing on LPRD or GERD in children were excluded. According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements,[16] the article selection is summarized in the flowchart in Figure 1. The results of the search strategy were reviewed for relevance. The author provided a critical analysis of the literature findings through a discussion based on the pharmacological and physiological properties of medications (eg, PPIs, prokinetics, alginate, or antacids) to provide to otolaryngologists' clinical relevance for prescribing medication for LPRD patients. Ethics committee approval was not required for this review.

RESULTS AND FINDINGS

Primary treatments

Fifty-five studies met the inclusion criteria (Figure 1).[9,11,12,17–68] Some teams published several studies using an enlarged database, which led the author to consider only the largest cohort study. The features of the studies are summarized in Table 1. Most studies were prospective, uncontrolled studies, including patients with suspected LPRD without confirmation of the diagnosis through objective diagnostic tools (Table 2). The diagnosis was primarily suggested using the association of Reflux Symptom Index (RSI) > 13 and reflux finding score (RFS) > 7 ($n = 13$, 23.6%). In 15.5% of studies, the teams used different RSI and RFS cutoffs than those validated in the initial studies.[2] The LPRD diagnosis was based on the occurrence of pharyngeal reflux events at the 24-hour HEMII-pH in only two studies, which retrospectively adhered to the Dubai Criteria.[1,54,58] The therapeutic regimens are reported in Table 3. Diet and behavioral changes were recommended to patients in 38 (69.1%) studies (Table 1). Sixty-seven therapeutic regimens were used in the LPRD studies conducted in the past 20 years with nine durations (Table 3). PPIs were used as primary or in combined drug association in 70.1% and 23.9%, respectively. There was an important variability of molecules, doses, and regimens. Alginates and antacids were used as single therapy or in association with other drugs in 10.5% and 3.0% of cases, respectively. The other associations included PPIs with H2-blockers (1.5%), prokinetics (10.4%), mucolytics (1.5%), and potassium-competitive acid blockers (1.5%), respectively. The studies evaluating alginate or antacid efficacy were mostly published in the past 5 years, which highlights an evolution of trends in clinical studies related to LPRD treatments (Table 1). The literature dedicated to the comparison of several medications in LPRD is still poor, and the lack of prospective controlled randomized studies comparing diet and lifestyle changes, PPIs, alginates, and antacids in patients with a demonstrated LPRD limits the drawing of reliable conclusions.

Physiological consideration

The physiology of LPRD can be investigated with clinical tools documenting the esophageal functioning, the microscopic structure of upper digestive mucosa, and devices detecting gastroduodenal content in the upper aerodigestive tract.[2–4] The HEMII-pH testing is the main clinical tool to confirm the LPRD diagnosis through the identification of more than one esophago-pharyngeal reflux events, but HEMII-pH can be used to investigate the profile of LPRD.[1] In that way, recent studies using 24-hour HEMII-pH support that esophago-pharyngeal reflux events are mainly gaseous, weakly acid, or alkaline, and they occur daytime and upright.[69,70] The pH of esophago-pharyngeal events appears to progressively increase throughout the reflux process from the distal to the proximal esophagus, given the bicarbonate secretion by esophageal mucosa, leading to this weakly acid profile of LPRD.[1,69] In two recent studies, the authors observed that the saliva pH of patients with LPRD is more alkaline than the pH of healthy individuals, which could be attributed to the mucosa defense mechanisms (bicarbonate secretion).[3,71] The most recent enzyme studies report that LPRD patients report higher saliva concentrations of pepsin,[72] bile salts,[73,74] elastase,[3] and potentially trypsin[4] compared with healthy individuals. In this context, some refluxed gastroduodenal enzymes could be activated in weakly acid and alkaline environments, leading to mucosa injuries and related symptoms. In addition, the alkaline saliva pH can support a reduced activation of extracellular pepsin, while PPIs are of great effectiveness regarding the alkaline mucosa environment. The upper aerodigestive tract weakly

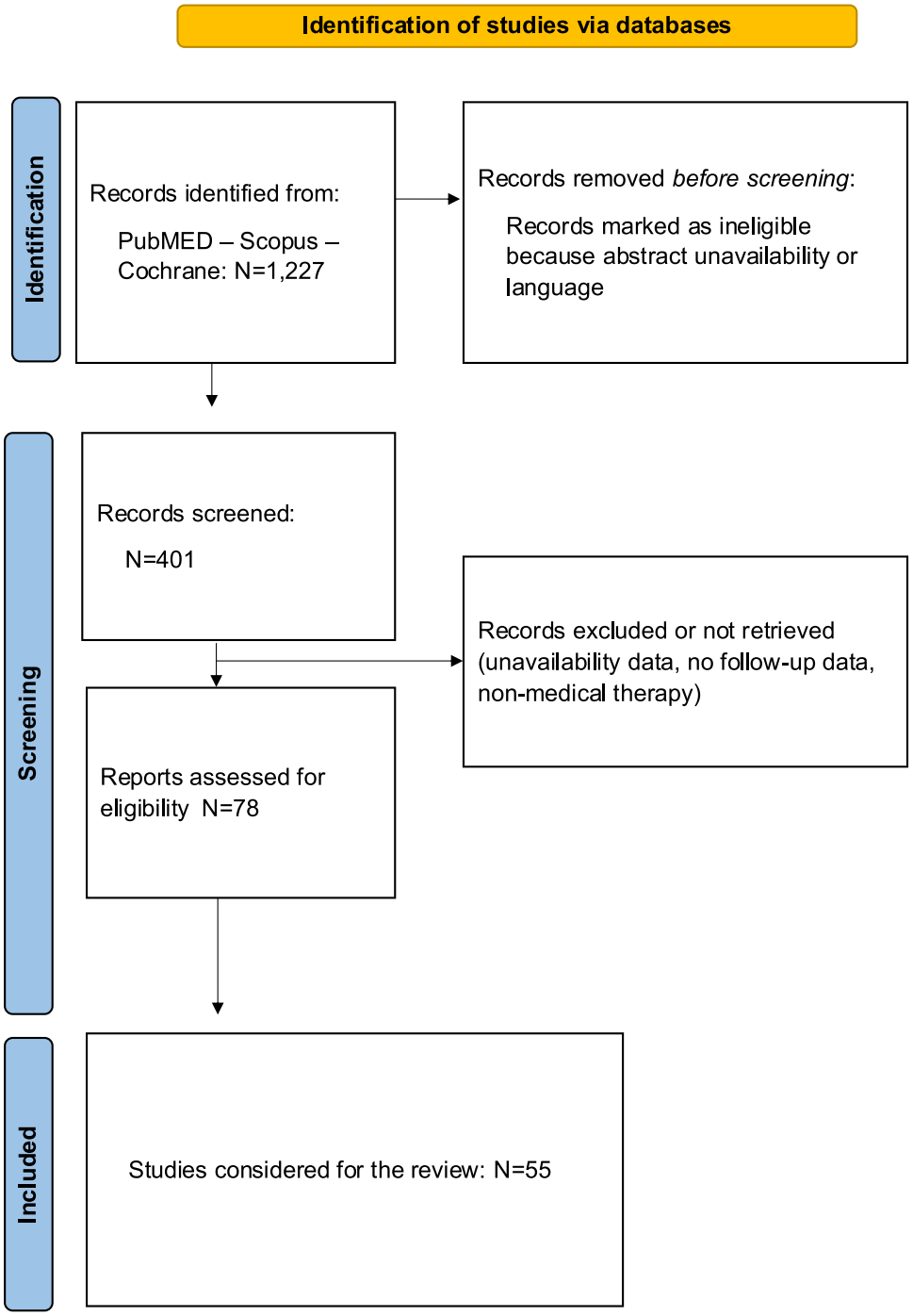

FIGURE 1. Chart flow. Some studies have been excluded from the eligibility step to the final inclusion step for the following reasons: consideration of alternative treatment associating drugs and alternative medicine such as acupuncture, auriculotherapy, etc; lack of details for the treatment/diagnosis criteria (not sure that LPRD was the disease); and overlap with other cohort studies from the same group.

acid and alkaline pH environment of LPRD patients is an important finding in the understanding of medication effectiveness and indications in LPRD.

Pharmacological consideration

PPIs

Chemical structure and pharmacological outcomes. The pharmacological properties of PPIs are important for understanding the LPRD clinical findings. PPIs are weak bases that are enabled to accumulate selectively in the acidic space of the secretory canaliculus of the stimulated parietal cells of the stomach.[75] PPIs are activated in an acid environment, and they convert to sulfenic acids or sulfenamides that react covalently with one or more cysteines accessible from the luminal surface of the gastric H,K-ATPase. The covalent binding leads to the inhibition of pumps and related acid secretion.[75] The covalent inhibition of the H,K-ATPase was found to be

TABLE 1.
Patient Features

References	Design	*N*	F/M	Age	Diagnosis	Outcomes	Medication	Diet	TD	Results
Siupsinskiene and Adamonis[17]	MCS	113	87/26	40.4	Symptoms and signs	CSS	Omeprazole 20 mg 1/d	+	5 we	pre > post
Garrigues et al[18]	MUnCS	91	67/24	40	Symptoms and signs	CSS and CFS	Omeprazole 20 mg 2/d	+	24 we	pre > post
Qadeer et al[19]	MUnCS	72	40/32	54.7	Single-probe pH testing	CSS and CFS	Omeprazole 40 mg 2/d	NP	16 we	pre > post
Park et al[20]	MCS	85	56/29	49	Symptoms and signs	CSS and CFS	Lansoprazole 60 mg 2/d Lansoprazole 30 mg 2/d	+	16 we	pre > post
Vaezi et al[21]	Placebo RCT	95	47/48	51.5	Dual-probe pH testing	CPL	Omeprazole 20 mg 2/d and Ranitidine 300 mg 1/d Esomeprazole 40 mg 1/d Esomeprazole 40 mg 2/d/ placebo	-	16 we	pre > post
Dore et al[22]	MUnCS	266	190/ 76	48	Symptoms	CSS	PPIs 2/d	+	12 we	pre > post
Reichel et al[23]	Placebo RCT	58	30/32	48.7	RSI > 13 and RFS > 7	RSI and RFS	Esomeprazole 20 mg 2/d/ placebo	-	12 we	pre > post
Lam et al[24]	Placebo RCT	82	59/23	46.8	RFS > 7	RSI and RFS	Rabeprazole 20 mg 2/d/ placebo	+	18 we	pre > post
Ezzat et al[25]	Placebo RCT	87	34/53	33.5	Symptoms and signs	RFS and CSS	Pantoprazole 40 mg 1/d + Itopride vs Pantoprazole + placebo	+	8 we	pre > post
Friedman et al[26]	Retrospective	143	86/57	53	Oropharyngeal pH testing	RSI	PPIs 20/40 mg 2/d	+	24 we	pre > post
Lee et al[27]	MUnCS	455	NP	51.9	Symptoms and signs	RSI and RFS	Rabeprazole 10/20 mg 1/d	+	12 we	pre > post
Naiboglu et al[28]	MUnCS	50	26/24	43.6	RSI > 13 and RFS > 7	RSI and RFS	Lansoprazole 30 mg 1/d	+	12 we	pre > post
Patigaroo et al[29]	MUnCS	50	30/20	38	RSI > 13 and RFS > 7	RSI and RFS	PPIs 2/d	NP	16 we	pre > post
Habermann et al[30]	MUnCS	1002	595/ 407	53	RSI > 9 and RFS > 7	RSI and RFS	Pantoprazole 40 mg 1/d/20 mg 2/d	NP	6 we	pre > post
Park et al[31]	MUnCS	100	52/48	55	RSI > 13 and RFS > 7	RSI and RFS	Omeprazole 20 mg 2/d	-	12 we	pre > post
Hunchaisri[32]	MCS	65	51/14	46	RSI > 13	RSI	Omeprazole 20 mg 2/d and Domperidone 10 mg 3/d	+	12 we	pre > post
Oridate et al[33]	MuCS	73	NP	NP	Symptoms	mRFS	Rabeprazole 10 mg 1/d	NP	4 we	pre > post

TABLE 1. *(Continued)*

References	Design	*N*	F/M	Age	Diagnosis	Outcomes	Medication	Diet	TD	Results
Pedersen and Eeg[68]	MPC	237	56/22		Symptoms and signs	Symptom CS	Diet	+	2 we	pre > post
			53/17			Sign CS	Omeprazole			pre > post
			63/26				Omeprazole + alginates			pre > post
Chun and Lee[34]	RCT	61	31/33	51.7	RSI > 13 and RFS > 7	RSI and RFS	Lansoprazole 30 mg 1/d and Itopride 50 mg, 3/d	NP	12 we	pre > post
Lien et al[35]	MUnCS	107	49/58	50	Triple-probe pH testing	RSI	Esomeprazole 40 mg 2/d	+	12 we	pre > post
Beech et al[36]	MUnCS	74	NP	NP	RSI > 13	RSI	Lansoprazole 30 mg 2/d	+	24 we	pre > post
Lee et al[37]	MuUnCS	180	82/98	52.8	Symptoms and signs	RSI and RFS	Lansoprazole 15 mg 2/d	+	12 we	pre > post
Chappity et al[38]	RCT	234	199/115	36.9	RSI > 13	CSS	Omeprazole 20 mg 2/d	+	12 we	pre > post
Wan et al[39]	MCS	58	21/37	42.4	Dual-probe pH testing	RSI and RFS	Esomeprazole 20 mg 2/d	+	4 we	pre > post
Semmanaselvan et al[40]	MUnCS	50	28/22	45.3	RSI > 13 and RFS > 7	RSI and RFS	Rabeprazole 20 mg 1/d Domperidone 10 mg 3/d	NP	12 we	pre > post
Ozturan et al[41]	MCS	65	NP	NP	Symptoms	RSI and RFS	Esomeprazole 20 mg 2/d	+	8 we	pre > post
Gupta et al[42]	Retrospective	188	140/48	57	Symptoms and signs	RSI and RFS	(Es)omeprazole 20 mg 2/d	+	10 we	pre > post
Batioglu et al[43]	MUnCS	84	66/18	43.1	RSI > 13 and RFS > 7	RSI and RFS	Lansoprazole 30 mg 2/d	NP	12 we	pre > post
Joshi et al[44]	MUnCS	100	54/46	41.5	Symptoms and RFS > 7	RSI and RFS	Omeprazole 20 mg 2/d	+	24 we	pre > post
Tseng et al[11]	Placebo RCT	79	49/30	47.9	RSI > 10 and RFS > 5	RSI and RFS	Alginate/placebo	+	8 we	pre > post
Lechien et al[45]	MUnCS	80	40/40	51.3	RSI > 13 and RFS > 7	RSI and RFS	Pantoprazole 20 mg 2/d	+	12 we	pre > post
Wilkie et al[12]	MPC	72	39/33	64.5	RSI > 10	RSI	Gaviscon advance 3/d PPIs and Gaviscon advance 3/d	+	12 we	pre > post
Bhargava et al[46]	MUnCS	240	116/124	34.3	RSI > 13 and RFS > 7	RSI and RFS	PPIs 2/d	NP	12 we	pre > post
Lee et al[67]	MUnCS	32	23/9	56.0	MII-pH	RSI and RFS	Lansoprazole 15 mg 2/d and Baclofen 10 mg 3/d	+	12 we	pre > post

TABLE 1. *(Continued)*

References	Design	*N*	F/M	Age	Diagnosis	Outcomes	Medication	Diet	TD	Results
Yoon et al[47]	RCT	100	44/56	58.8	Symptoms and signs	RSI and RFS	Ilaprazole 10 mg 1 or 2/d Ilaprazole 10 mg 2/d and Mosapride 5 mg 3/d	+	12 we	pre > post
Divakaran et al[48]	MUnCS	120	67/53	39	RSI > 13 and RFS > 7	RSI and RFS	Esomeprazole 40 mg 2/d and Domperidone 10 mg 3/d	+	4 we	pre > post
Ceylan et al[49]	MUnCS	60	35/25	40.0	RSI > 13 and RFS > 7	RSI and RFS	Pantoprazole 40 mg 2/d	+	8 we	pre > post
Junaid et al[50]	MUnCS	102	58/44	41.8	Symptoms and signs	RSI and RFS	Omeprazole 40 mg 1/d	+	12 we	pre > post
Kulekci et al[51]	MUnCS	67	56/11	44.2	Symptoms and signs	CSS	Lansoprazole 30 mg 1/d	+	4 we	pre > post
Chae et al[52]	RCT	116	79/37	57.2	RSI > 12 and RFS > 6	RSI and RFS	Rabeprazole 10 mg 2/d vs Rabe + Acebrophylline 200 mg 2/d	+	12 we	pre > post
Boom et al[53]	MUnCS	101	52/49	49.4	RSI > 13 and RFS > 7	RSI and RFS	Esomeprazole 40 mg 1/d	NP	8 we	pre > post
Kim et al[54]	MUnCS	80	49/31	56.4	HEMII-pH	RSI and RFS	PPIs 2/d	+	8 we	pre > post
Pizzorni et al[9]	RCT	50	35/15	69.3	RSI > 12 and RFS > 6	RSI	Magnesium alginate 3/d Omeprazole 20 mg 1/d	+	8 we	pre > post
Jain et al[55]	MUnCS	50	32/18	41.4	Dual-probe pH testing	RSI and RFS	Pantoprazole 40 mg 2/d and Mosapride 5 mg 3/d	NP	6 mo	pre > post
Mathew and Shilpa[56]	RCT	100	58/42	45.6	RSI > 13 and RFS > 7	RSI and RFS	Pantoprazole 40 mg 2/d Pantoprazole 40 mg 2/d and Sodium alginate 2/d	+	8 we	pre > post
Liu et al[57]	MUnCS	60	34/26	43.3	RSI > 12 and RFS > 6	RSI and RFS	Esomeprazole 20 mg 2/d	+	12 we	pre > post
Lechien et al[58]	MuUnCS	237	138/99	51.3	HEMII-pH testing	RSS and RSA	Pantoprazole 20 mg 2/d and Sodium alginate 3/d or Magaldrate 3/d	+	12 we	pre > post
Han et al[59]	MUnCS	135	68/67	43	Oropharyngeal pH testing	RSS	PPIs 2/d	NP	8 we	pre > post
Kwon et al[60]	MuUnCS	288	164/124	55.1	RSI > 12 and RFS > 6	RSI	Esomezol 49.3 mg 1/d	+	12 we	pre > post
Muddaiah et al[61]	MUnCS	200	104/96	48	Symptoms and signs	RSI and RFS	Pantoprazole 40 mg 2/d	+	8 we	pre > post
Kapil et al[62]	MUnCS	128	73/55	39	RSI > 12 and RFS > 6	RSI and RFS	Pantoprazole 40 mg 2/d	NP	6 mo	pre > post

TABLE 1. (*Continued*)

References	Design	*N*	F/M	Age	Diagnosis	Outcomes	Medication	Diet	TD	Results
Paramasivam et al[63]	MUnCS	96	NP	42.5	RSI > 13	RSI	PPIs	+	6 mo	pre > post
Kim et al[64]	RCT	136	NP	NP	RSI > 13 and RFS > 6	RSI and RFS	Fexuprazan 40 mg 1/d	+	8 we	pre > post
Kim et al[65]	Retrospective	22	1/21	52.6	MII-pH-granuloma	RSS-12 RSI and RFS	Omeprazole 40 mg 1/d PPI	NP	3-6 mo	pre > post
Suda et al[66]	MUnCS	100		18-75	RSI > 13	RSI	PPI	+	8 we	pre > post

Note that Ezzat et al recommended speech therapy as well. *Abbreviations:* CFS, composite finding score (not validated); CSS, composed symptom score; F/M, female/male; mo, months; MPC, monocentric prospective controlled; M(u)UnCS, monocentric (multicentric) uncontrolled study; N, number; NP, not provided; PPI, proton pump inhibitor(s); RCT, randomized controlled trial; RFS, reflux finding score; (m) RSI, (modified) Reflux Symptom Index; RSA, reflux sign assessment; RSS, reflux symptom score; TD, treatment duration; we, week(s).

TABLE 2.
Diagnosis Methods in Studies

Diagnosis methods	*N*	%
Symptoms (no validated PROM)	3	5.4
Symptoms and signs (no validated PROM/instrument)	12	21.8
Validated PROMs		
Reflux Symptom Index		
RSI > 10	1	1.8
RSI > 13	5	9.1
Validated Sign Instruments		
Reflux Finding Score		
RFS > 7	2	3.6
Association of Validated PROM and Instrument		
RSI > 13 and RFS > 7	13	23.6
RSI > 12 and RFS > 6	5	9.1
RSI > 13 and RFS > 6	1	1.8
RSI > 9 and RFS > 7	1	1.8
RSI > 10 and RFS > 5	1	1.8
Objective Tools		
Single-probe pH monitoring	1	1.8
Dual-probe pH monitoring	3	5.4
Triple-probe pH monitoring	1	1.8
MII-pH	2	3.6
Oropharyngeal pH monitoring	2	3.6
HEMII-pH	2	3.6
Total	55	100

Abbreviations: (HE)MII-pH, (hypopharyngeal-esophageal) multichannel intraluminal impedance-pH monitoring; N, number; PROMs, patient-reported outcome questionnaire(s); RFS, reflux finding score; RSI, Reflux Symptom Index.

more effective than the receptor antagonists (H2-blockers) in suppressing gastric acid secretion.[76,77] The covalent binding to the H,K-ATPase makes the duration of PPIs longer than expected from the blood levels,[75] and the PPI blood concentration does not reflect its activity.

Pharmacologically, the area under the blood concentration-time curve (AUC) is a predictor of the gastric antisecretory effect and the pharmacodynamic response.[75] For this reason, the pharmacological studies comparing the effectiveness of PPIs in reflux diseases used the AUC rather than the blood concentration as an indicator of efficacy.[75] The increase in doses and the repeated administration of omeprazole or esomeprazole are associated with an increase in the maximal plasma concentration and the AUC in a nonlinear fashion.[78,79] Clinically, the most adequate time of PPI intake, doses, and the number of doses in LPRD patients can find a response in the pharmacological properties.

First, a one-morning dose of PPIs only inhibits 70% of the H,K-ATPase because not all pumps are active during the blood half-life of the PPIs (90 minutes).[75] Moreover, 20% of H,K-ATPase is newly synthesized over 24 hours with a greater pump synthesis during the night.[75] Then, the physiological knowledge supports that the bedtime administration of PPIs does not add to the inhibition of

TABLE 3.
Therapeutic Regimens

Therapeutic Regimen	*N*	%
Proton pump inhibitors (single therapy)	47	70.1
Omeprazole 20 mg 1/d	2	3.0
Omeprazole 20 mg 2/d	4	6.0
Omeprazole 40 mg 1/d	2	3.0
Omeprazole 40 mg 2/d	1	1.5
Esomeprazole 20 mg 2/d	4	6.0
Esomeprazole 40 mg 1/d	2	3.0
Esomeprazole 40 mg 2/d	2	3.0
Lansoprazole 15 mg 2/d	2	3.0
Lansoprazole 30 mg 1/d	2	3.0
Lansoprazole 30 mg 2/d	2	3.0
Lansoprazole 60 mg 2/d	1	1.5
Pantoprazole 20 mg 2/d	1	1.5
Pantoprazole 40 mg 2/d	5	7.5
Unspecified or another PPI 1/d	6	9.0
Unspecified or another PPI 2/d	8	11.9
Rabeprazole 10 mg 1/d	2	3.0
Rabeprazole 20 mg 2/d	1	1.5
Alginates		
Sodium/magnesium alginates 3/d	3	4.5
Antacids		
Magaldrate 3/d	1	1.5
Medication combinations		
PPIs and H2-blockers	1	1.5
PPIs and prokinetics	7	10.4
PPIs and alginates	4	6.0
PPIs and mucolytics	1	1.5
PPIs and antacids	1	1.5
PPIs and potassium-competitive acid blocker	1	1.5
PPIs and Baclofen	1	1.5
Total Regimens	67	100
Duration of treatment	*N* = 55	
2 we	1 (1.8)	
3 we	1 (1.8)	
4 we (1 month)	4 (7.3)	
8 we (2 months)	12 (21.8)	
10 we	1 (1.8)	
12 we (3 months)	24 (43.6)	
16 we (4 months)	4 (7.3)	
18 we	1 (1.8)	
24 we (6 months)	7 (12.7)	

The total number of therapeutic regimens was superior to the number of studies because some teams used several drug regimens. *Abbreviations:* d, day; N, number; PPI(s), proton pump inhibitors(s); we, weeks.

nocturnal acid breakthrough because the drug has disappeared by the time of nighttime acid secretion.[75] To date, it is recommended to take PPI in the morning in patients with acid LPRD.

Second, considering that about 70% of H,K-ATPase are activated by breakfast[75] and that the PPI is taken at least 30 minutes beforehand, the steady-state inhibition on once-a-day dosing is about 66% of maximal acid output. The intake of a morning dose and an evening dose before meals (twice-daily PPI regimen) results in about 80% inhibition of maximal acid output, while an increase of the PPI dose has virtually no effect once the optimal dosage has been reached.[75] This point was supported by numerous bioavailability studies, which suggested that the intake of one or two doses of omeprazole in a day led to bioavailabilities of 40% and 60%, respectively.[78] For esomeprazole (20 mg), the bioavailabilities of single and twice-daily doses are 50% and 68%, respectively.[78] The pharmacological superiority of twice-daily PPI over once-daily is clinically supported by Park et al, who observed better symptom relief in suspected LPRD patients treated with twice-daily PPIs compared with those treated with once-daily PPIs.[20] However, the study of Park et al is the only one conducted in otolaryngology for comparing once-versus twice-daily PPI effectiveness, which limits the establishment of reliable clinical conclusions.

Third, PPIs need to be taken at least 30-60 minutes before eating. The bioavailability of esomeprazole was significantly reduced (50%) when taken within 15 minutes before eating compared with fasting conditions.[78,80] Rabeprazole is the only one PPI that can be taken during meals regarding the little impact of diet on its bioavailability.

Differences between PPI molecules and personalized medicine

PPIs are composed of a substituted pyridine and a benzimidazole. The various PPIs differ for the substituents on the pyridine or benzimidazole, which is associated with different cysteine bindings and somewhat different pharmacokinetic properties (ie, time- and dose-dependent bioavailability, metabolic pattern, interactions, and genetic variability).[75,81,82] The oral bioavailability, blood half-life, AUC, clearance, metabolism, and plasma concentration properties are summarized in Table 4. The awareness of the various PPI pharmacological properties can be useful in otolaryngology practice in making personalized medicine. On the one hand, considering that PPIs are metabolized in the liver by the CYP2C19 and accessory CYP3A4, patients with hepatic insufficiency have a prolonged half-life of most PPIs, and it is recommended to use esomeprazole rather than the others given its better tolerability to hepatic disorder.[82,83] On the other hand, the cytochrome activity and the PPI metabolism can be influenced by ethnicities, with a prevalence of 10%-20% of poor metabolizers in Asian populations.[75,81] The administration of once-daily omeprazole (20 mg) leads to 3-to-5- and 5-to-10-time higher plasma concentration peak and AUC in poor metabolizers compared with normal metabolizers,[78] which can indicate a need for a decrease of PPI doses to minimize the risk of toxicity associated with long-term PPI use at higher plasma concentrations.[81] Aging and gender are additional outcomes that could be considered in the PPI prescription. Thus, the metabolism of pantoprazole and esomeprazole is not influenced by aging, which supports their use in elderly patients (Table 4). Concerning gender, the current data of

TABLE 4.
Pharmacological Findings of Medications

	Proton pump inhibitors					Alginates	Antacids
Pharmacology	Omeprazole (20 mg)	Pantoprazole (40 mg)	Lansoprazole (30 mg)	Esomeprazole (40 mg)	Rabeprazole (20 mg)	Sodium	Magaldrate
Oral bioavailability	40%-60%	77%	80%-90%	89%	52%		
Influence of the diet on bioavailability	Yes	Yes	Yes	Yes	No		
Area under the curve	0.2-2.0	1-15.9	1.7-5.2	7.3-12.6	0.8-2.2		
Half-life (hours)	0.5-1.2	0.8-2.0	0.9-2.1	1.1-1.6	0.6-1.4		
Maximal plasma concentration (μmol/L)	0.23-23.2	2.87-8.61	1.62-3.2	4.7-5.1	1.14	Local action	Local action
Time for maximal plasma concentration (hours)	1-2	2-4	1.2-2.1	1.0-3.5	3-5		
Plasmatic protein bind (%)	97%	98%	87%	97%	97%		
Clearance (mL/min) L/h/kg	400-620	90-225	400-650	160-330	98		
Metabolism							
Primary/secondary enzymes	CYP2C19/ CYP3A4	CYP2C19/CYP3A4	CYP2C19/CYP3A4	CYP2C19/CYP3A4	CYP2C19/ CYP3A4	No hepatic	No hepatic
Aging influence	Yes	Poor	Yes	Poor	Yes	metabolism	metabolism
Ethnicity influence	Yes	Yes	Yes	Yes	Yes		
Poor metabolizers (Europe-Asia)	3%-15%-20%	3%-15%-20%	2%-6%-10%-20%	3%-15%-20%	2.7%-6.1%-15%-20%	No	No
Clinical influence of diseases							
Renal/hepatic insufficiency	No-mild	No-mild	No-mild	No-no	No-mild	Yes (severe)- no	Yes (severe)- no
Breastfeeding/pregnancy counter-indications	No-ND	Yes-ND	NS-NS	NS-NS	NS-NS	No-no	No-no

The data provided in this table were collected from international studies, the national pharmacological recommendation database of France (Gouv.) and Belgium (CPIB). Some results are presented as ranges due to inconsistencies between studies. The area under the curve data are correlated with the acid suppression. *Close monitoring of the prothrombin time or INR may be required. *Abbreviations:* ND, not demonstrated; NS, no significant study; PPIs, proton pump inhibitors.

the literature are limited about the PPI effects in pregnancy and breastfeeding females, and to date, it is preventively recommended to avoid PPIs in these patient populations. Females have higher gastrin release following PPI therapy compared with males.[78] The AUC of females is commonly 30% higher than that of males when receiving a single dose of PPIs. Moreover, females have a higher risk of PPI overuse and adverse events than males.[78] In this context, females should potentially benefit from receiving lower dosages of PPIs than those administered to males.[78] Finally, the drug interaction is another point that can be considered in the prescription of PPIs in otolaryngology. The studies dedicated to the drugs potentially interacting with PPI molecules are flawed, and most recommendations are based on cautious attitude. Currently, it is recommended to pay attention to the use of PPIs in patients treated with Human immunodeficiency virus protease inhibitors, oral iron, warfarin, and clopidogrel seem, however, to be counter-indicated (Table 5).

Duration and resistance to PPI therapy

The duration of PPI therapy varies from 2 weeks to 6 months in studies (Table 1). To date, there are no controlled studies investigating upper aerodigestive tract mucosa healing, finding, and symptom relief according to the duration of PPIs. However, it seems that a therapeutic duration of one month is enough to have a significant medication response.[84] In this recent study where authors prescribed a combination of PPI, alginate, and magaldrate, patients without symptom improvement after 1 month of treatment did not experience additional symptom change in the second and third post treatment months.[84] In gastroenterology literature, the esophageal mucosa is healed in 78% of patients after 1 month of esomeprazole 40 mg.[78] Others showed that 93.7%-94.1% of GERD patients treated with 40 mg of esomeprazole were healed after 8 weeks of treatment, while 84.2%-86.9% of patients reported similar results after 8 weeks of 20 mg of omeprazole.[85,86] Others did not report a significant difference between 40 mg of esomeprazole and 40 mg of pantoprazole,[87] which supports the low interest in changing PPI molecule in case of recalcitrant GERD symptoms. The low impact of increasing doses was supported, considering that an adequate mucosa healing of reflux esophagitis is commonly achieved when the intragastric pH is greater than 4 for 16 hours per day, while an increase in the duration of acid secretion has no additional effect.[75] Naturally, these findings are related to GERD, and esophagus studies cannot be applied to LPRD and related laryngeal and pharyngeal mucosa.[88] However, considering the higher resistance of the esophageal nonkeratinized epithelium compared with the pharyngeal and laryngeal epithelia toward mechanical and chemical aggressions,[89] it could be suspected that the protective and healing effect of PPIs on laryngopharyngeal mucosa is at least comparable to those on esophageal mucosa.

In summary, the inhibition of gastric acid secretion can increase the pH of esophago-pharyngeal reflux events, inhibiting the pepsin activity in laryngopharyngeal mucosa.[2,4] The PPIs can be prescribed twice daily at fasting time (at least 1 hour before meals), which is pharmacologically[75,79] and clinically[20] more effective than once-daily high dose for patients with evidence of acid GERD or acid LPRD. The increase of PPI doses in patients with recalcitrant symptoms is pharmacologically associated with little advantage on gastric acid secretion and, consequently, can be avoided.

Histamine H2-receptor antagonists

The H2-blockers were used in a few studies. The low use of H2-blockers, especially in Europe, is related to the superiority of PPIs over H2-blockers in GERD.[75,76] Precisely, H2-blockers decrease the production of stomach acid with less favorable pharmacological properties (eg, half-life) and clinical outcomes than PPIs in GERD therapy,[74] on-demand therapy for transient symptoms,[76] or in upper gastrointestinal bleeding.[90] In LPRD, H2-blockers have been not included in the primary medication regarding best practice[91] or guideline[1] papers.

Alginates

Alginate is an anionic polysaccharide occurring in brown algae. There are various alginates approved by the food and drug administration, eg, sodium alginate and calcium alginate. They rapidly grew in popularity for the LPRD treatment in the past few years regarding their protective effect on mucosa against refluxed gastroduodenal enzymes that are activated in acid, weakly acid, and alkaline environments.[3,4] Physiologically, alginate reduces reflux via its floating, foaming, and viscous properties, creating a mechanical barrier, or a “raft” in reaction with acid (conversion of bicarbonate into carbon dioxide), which displaces the postprandial acid pocket. The acid pocket is a short zone of unbuffered, highly acidic gastric juice, which accumulates in the proximal stomach after meals. Because a significant number of liquid, gaseous, and mixed reflux events originate from this stomach zone, alginate drugs can be effective on both GERD and LPRD through a common reduction of the number and duration of reflux events.[92,93] The formation of the raft is rapid, occurring within a few seconds after the intake, which is faster than PPIs or H2-blockers.[92] In the case of GERD, the raft can be refluxed into the distal esophagus, which is associated with fewer injuries than acid reflux due to the neutral pH of the raft. From a clinical standpoint, alginate should be more effective than antacids in controlling postprandial esophageal acid exposure and relieving GERD typical symptoms, including heartburn, regurgitation, vomiting, and belching, with longer duration. Double-blind randomized controlled trials demonstrated the superiority of alginate over placebo in terms of regurgitations and heartburn symptoms in patients with erosive and nonerosive reflux diseases,[94] and noninferiority compared with PPIs in nonerosive reflux

TABLE 5.
Drug Interactions

Drugs* potentially interacting with	Omeprazole (20 mg)	Pantoprazole (40 mg)	Lansoprazole (30 mg)	Esomeprazole (40 mg)	Rabeprazole (20 mg)	Alginates	Magaldrate
HIV protease inhibitor	+	+	+	+	+		
Methotrexate (high doses)	+	+			+		
Ketoconazole, ampicillin	+	+	+		+		
Oral iron	+	+	+	+	+		
Itraconazole and Ketoconazole	+	+	+	+			+
Disulfiram		+					
Oral contraceptives			+				
Warfarin	+	+	+	+	+		
Clopidogrel	+	+	+	+	+		
Phenytoin	+		+	+			
Aluminum/magnesium hydroxide			+				
Clarithromycin	+		+				
Digoxin	+		+	+	+	+	+
Sucralfate			+				
Theophylline			+				
Carbamazepine	+						
Cyanocobalamin	+						
Cyclosporin	+						
Fluvastatin/atorvastatin	+			+			
Tacrolimus	+		+				
Citalopram/diazepam				+			
Imipramine/clomipramine				+			
Acid beverages (soda, juices, coffee, and alcohol)							+
Tetracyclines and quinolones						+	+
Indomethacin and isoniasides							+
Coumaric							+
thyroid hormone (L-thyroxin)	+	+	+	+	+	+	+
Neuroleptics						+	
Penicillin, chloroquine						+	
Beta-blockers, diphosphonates						+	

According to international studies, French and Belgian pharmacological recommendation databases,[78] the interactions between medications were highly suspected and, in most cases, were not totally demonstrated.
HIV, Human immunodeficiency virus

disease patients.[95] In the LPRD literature, only one randomized controlled trial was conducted in patients with suspected LPRD, reporting that alginate can reduce the number of proximal esophageal reflux events, while the authors did not demonstrate the superiority of alginate over placebo.[11] Importantly, the authors recommended diet, lifestyle, and behavioral changes in both groups, which could bias the evaluation of potential differences between groups. To date, it is recommended in LPRD to take alginate a few minutes after the meals to reduce the number of transient esophageal and pharyngeal reflux events, which mostly occurred in the 1-2 hours post meals.[68,70] The duration of alginates ranges from 30 minutes to 2 hours, which clinically appears sufficient to protect the mucosa from reflux events.[96] The pharmacological properties and interactions of alginates are highlighted in Tables 4 and 5.

Antacids

Several antacids are approved by the food and drug administration and are available on the American and European markets. Magnesium hydroxide and aluminum oxide are both antacids used in GERD.[97] Pharmacologically, the combination of aluminum and magnesium hydroxide (magaldrate) neutralizes the acidity of the gastric pocket, forms a protective coating for gastroesophageal mucosa, and is a chelator of pepsin and bile acids.[78] In theory, the chelation of pepsin and bile acids is an important mechanism for LPRD patients regarding the laryngopharyngeal mucosa inflammation induced by the toxicity of bile acids and pepsin.[98] Algeldrate is another antacid that neutralizes acid, increasing the stomach pH and inactivating the lysolecithin and bile salts. Lysolecithin is formed when pancreatic juice and bile mix in the duodenum. In clinical studies, magaldrate and algeldrate have been used as primary treatment of weakly acid or alkaline LPRD in recent studies,[10,58,84] and they were associated with symptom relief in patients with a primary or recalcitrant LPRD.[13] The recent data objectifying the presence of bile acids in the saliva or LPRD patients strengthen the use of antacids as chelators of saliva gastroduodenal components.[3,73,74,99] However, to date, there are no controlled studies comparing antacids with alginate or PPIs in patients with a demonstrated LPRD. Similarly to alginate sodium, antacids can be taken post meals, and they have a duration of action of approximately 1.5 hours without an acid-rebound effect.[78] The pharmacological properties and interactions of magaldrate are reported in Tables 4 and 5.

Prokinetics and transient lower esophageal sphincter relaxation inhibitors

The current prokinetics (eg, metoclopramide, domperidone, cisapride, and tegaserod) are physiologically interesting for both GERD and LPRD because they increase the esophageal peristalsis, esophageal acid clearance, and basal sphincter pressure, and they facilitate the gastric emptying time.[78] In GERD consensus and guidelines, they are not commonly prescribed as a single therapy given their adverse events and the lack of superiority over PPI.[92,100,101] In the LPRD literature, Ezzat et al reported better symptom relief in suspected LPRD patients treated with PPIs and itopride compared with those receiving PPI and placebo.[25] The interest in prokinetics in suspected LPRD was corroborated by Chun and Lee, who reported a better reduction of RSI in patients treated with lansoprazole and itopride compared with those treated with lansoprazole only.[34] The importance of prokinetics in LPRD was mitigated by the findings of Yoon et al, who did not observe the superiority of PPI and mosapride over PPI only in symptom relief of suspected LPRD patients.[47] However, in this study, the authors determine a potential benefit of adding mosapride to PPIs for obese patients. The controversial results in the literature can be related to the existence of several profiles of LPRD patients. Indeed, physiologically, esophageal dysmotility has been identified in 43% of LPRD patients,[102] which can contribute to LPRD symptoms, while in other case series, patients have isolated LPRD without esophageal dysmotility.[103] The assessment of prokinetics in further studies makes sense considering a personalized medicine approach for patients with a demonstrated LPRD at the 24-hour HEMII-pH and esophageal dysmotility at the high-resolution manometry. The other medications evaluated in GERD (eg, potassium-competitive acid blockers, GABA-receptor agonists, metabotropic glutamate receptors, cannabinoid receptor-1 agonist/antagonist, and neuromodulators) were not discussed in the present review according to the lack of evidence and clinical studies conducted in the LPRD literature.

Discussion and future directions

In most studies, the therapeutic regimens were based on the GERD evidence, and the pathophysiological differences between LPRD and GERD were rarely considered. Most clinical studies included in the present review reported significant reduction of symptom scores after a PPI therapy, which can be explained by an effect of PPIs on the acidic LPRD that is a part of the LPRD patient population. Despite significant statistical improvement, a substantial part of patients are nonresponders to PPIs.[8] Then, the recent advancements in the understanding of the LPRD pathophysiology can support the moderate effectiveness of PPIs and the potential role of GERD-alternative treatments (eg, alginates or antacids) in LPRD. In medicine, evidence-based practices are commonly based on the conduction of controlled randomized clinical trials comparing several therapeutic regimens. However, in the case of LPRD, the consideration of personalized therapies based on the LPRD features at the 24-hour HEMII-pH could make sense regarding the heterogeneity between patients in terms of types of refluxes (acid, weakly acid, and alkaline), time of reflux events, and esophageal dysmotility findings. About the refluxed enzymes, personalized therapies need to consider that pepsin can be activated in an extracellular environment through an internalization into the Golgi

apparatus where the weakly acidic pH can reactivate the pepsin, leading to intracellular damages.[98] For bile salts, conjugated bile salts are more active in alkaline environments, while nonconjugated bile salts are more active in acid environment. The enzyme activation findings can indicate the use of alginate or antacids in patients with bile salts in the saliva. Before conducting large-cohort studies implementing personalized medicine approaches, some additional studies are needed to evaluate the stability of the LPRD profile at the HEMII-pH from one day to the other (48-hour or 96-hour HEMII-pH), and the determination of the key roles of all gastro-pancreatico-duodenal enzymes (eg, elastase, bile acids, pepsin, and trypsin) in the development of inflammation and related symptoms. Moreover, future policies are needed to improve the pharmacological knowledge of otolaryngologists given the lack of awareness of otolaryngologists toward the benefits of antacids and alginates as alternative LPRD treatments.[5,14]

CONCLUSION

The pharmacological and physiological findings of this review can reasonably support the notion that alternative GERD therapies (alginate, antacids) could take a significant place in the treatment of primary or recalcitrant LPRD. Future studies are needed to confirm the stability of the LPRD profile at the HEMII-pH and the role of digestive enzymes in the development of upper aerodigestive tract mucosa inflammation and symptoms.

Author Contributions

Jerome R. Lechien: Design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; 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. **J.R. Lechien:** Design, literature research, and writing.

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