The Efficacy of Proton Pump Inhibitor Therapy for Treating Laryngopharyngeal Reflux: A Systematic Review

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Abstract

Background: Laryngopharyngeal reflux (LPR) is the backflow of stomach contents into the throat. The current standard of care is to treat patients with a proton pump inhibitor (PPI) twice daily for up to 6 months or longer. Two meta-analyses were completed in 2006 and found no evidence PPI therapy is better than placebo for chronic laryngitis. Since that time new tools have been created to measure outcomes in this field of research, the Reflux Finding Score (RFS) and Reflux Symptom Index (RSI). Using these standardized measures are researchers able to demonstrate PPI therapy is efficacious in the treatment of LPR?

Method: An exhaustive literature search using the Medline, EBMRM, and CINAHL search engines was conducted from 2006-present with the following search terms: laryngopharyngeal reflux, proton pump inhibitors, extraesophageal, laryngitis, globus, throat clearing, and chronic cough. Randomized controlled trials comparing PPI to placebo for the treatment of laryngopharyngeal reflux in adults were included. Trials were excluded if completed before 2006 or if they were previously evaluated in a meta-analysis. Studies were evaluated for quality using the GRADE criteria.

Results: Three studies met inclusion criteria and were evaluated in this systematic review. A double-blind, randomized, placebo-controlled trial with 82 participants demonstrated a statistically significant reduction in the total RSI scores after 12 weeks of treatment, this effect disappeared once treatment was stopped. Another double-blind, randomized, placebo-controlled trial with 41 participants found no difference from baseline in any of their outcome measures. Finally a double-blind, randomized, placebo-controlled trial found statistically significant reduced RSI at week 12. This was the only study able to demonstrate improvement in the RFS after 12 weeks of treatment.

Conclusion: The use of proton pump inhibitors for LPR continues to be a topic surrounded with controversy. Current research supports a trial of twice daily PPI for at least 3 months if the patient is also experiencing symptoms of GERD. Patients with throat symptoms alone are unlikely to find relief from PPI therapy and should be evaluated for other possible etiologies. The purpose of this review is to evaluate the latest placebo controlled RCT using the RFS and RSI to evaluate the efficacy of PPI therapy for LPR.

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The Efficacy of Proton Pump Inhibitor Therapy for Treating Laryngopharyngeal Reflux: A Systematic Review

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BIOGRAPHY
Wendy Kellam is a self-proclaimed Oregonian. She received a Bachelor of Science degree from the University of Wisconsin-Milwaukee in 1999 with a major in Communication Sciences and Disorders. She received a Masters of Art from Ball State University in 2001 in Speech Language Pathology. She spent her 10-year career as an SLP working with adults in acute care where she became captivated with the art of medicine. She would like to thank her partner in life Tom Slominski; without his patience, love and support her dream of becoming a PA would never have happened.
ABSTRACT

**Background:** Laryngopharyngeal reflux (LPR) is the backflow of stomach contents into the throat. The current standard of care is to treat patients with a proton pump inhibitor (PPI) twice daily for up to 6 months or longer. Two meta-analyses were completed in 2006 and found no evidence PPI therapy is better than placebo for chronic laryngitis. Since that time new tools have been created to measure outcomes in this field of research, the Reflux Finding Score (RFS) and Reflux Symptom Index (RSI). Using these standardized measures are researchers able to demonstrate PPI therapy is efficacious in the treatment of LPR?

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**Conclusion:** The use of proton pump inhibitors for LPR continues to be a topic surrounded with controversy. Current research supports a trial of twice daily PPI for at least 3 months if the patient is also experiencing symptoms of GERD. Patients with throat symptoms alone are unlikely to find relief from PPI therapy and should be evaluated for other possible etiologies. The purpose of this review is to evaluate the latest placebo controlled RCT using the RFS and RSI to evaluate the efficacy of PPI therapy for LPR.

**Keywords:** Laryngopharyngeal reflex, proton pump inhibitor, Reflux Symptom Index, Reflux Finding Score
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Table 1: GRADE Quality of Assessment and Summary of Findings

LIST OF ABBREVIATIONS

GERD  Gastroesophageal reflux disease
LPR   Laryngopharyngeal reflux
PPI   Proton pump inhibitor
RCT   Randomized controlled trial
RFS   Reflux Finding Score
RSI   Reflux Symptom Index
The Efficacy of Proton Pump Inhibitor Therapy for the Treatment of Laryngopharyngeal Reflux: A Systematic Review

BACKGROUND

Laryngopharyngeal reflux (LPR) is the backflow of stomach contents into the throat. It is commonly identified in otolaryngologist offices and diagnosed in almost 10% of their patient population. 1 Additionally, 50% of patients with voice disorders may have LPR. 2 Other terms used to describe this condition include: posterior laryngitis, extraesophageal reflux, reflux laryngitis, or supraesophageal reflux. Most clinicians are more familiar with gastroesophageal reflux disease (GERD), the backflow of stomach contents into the esophagus, which typically results in heartburn and regurgitation.

Patients with LPR and GERD differ in many ways. The majority of patients with LPR do not experience the characteristic heartburn of GERD; they tend to reflux during the day while upright versus at night while lying flat; and dysfunction is believed to originate in the upper esophageal sphincter versus the lower esophageal sphincter. 3

The larynx does not have the protective mechanisms of the esophagus to defend against acid exposure leading to irritation of the laryngeal mucosa and subsequent symptoms of chronic cough, hoarseness, dysphagia, globus (sensation of lump in the throat), frequent throat clearing and throat discomfort. 2,3 Making an accurate diagnosis can be difficult, as these same symptoms can be attributed to allergies, environmental triggers, smoking, and vocal abuse. 2,4 If left untreated LPR can lead to severe complications such as contact ulcers, granulomas and stenosis. 2 Some researchers are connecting LPR with increased incidence of adenocarcinoma of the larynx. 5,6

The position statement of the American Academy of Otolaryngology-Head and Neck Surgery 7 on LPR states that a diagnosis can be made based on a correlation between
Clinical symptoms of the disease and laryngeal findings on endoscopy. Signs specific for LPR include true/false vocal fold erythema/edema; posterior cricoid wall erythema; posterior commissure erythema/edema; and posterior pharyngeal wall erythema/edema. Often clinically no testing is undertaken and patients suspected of having LPR are treated empirically with proton pump inhibitor therapy and resolution of their symptoms is considered diagnostic. Despite its lack of sensitivity and specificity for LPR the gold standard for diagnosis is 24-hour double probe pH monitoring with the upper probe positioned in the hypopharynx. This test can be performed if a patient is refractory to proton pump inhibitor (PPI) treatment.

The treatment of LPR, recommended by otolaryngologists, advocates for lifestyle modification along with the initiation of PPI twice daily for a minimum of 6 months. The lack of randomized controlled trials supporting this treatment makes it controversial. The twice daily dosing is necessary because PPIs are unable to suppress acid for greater than 16.8 hours. Symptoms improve within 2-3 months but the laryngeal injury caused by the acid exposure requires prolonged treatment. Lifestyle modifications include: elevating the head of bed 6 inches, smoking cessation, low fat diet, weight loss, avoid lying down within 3 hours of eating, small frequent meals, bicarbonate gum chewing, preferential sleeping on the left side, and avoidance of refluxogenic foods. Finally, if patients have failed all avenues of treatment and symptoms are severe, laparoscopic fundoplication surgery may be warranted.

The American Gastroenterological Association reported poor sensitivity and specificity of endoscopy and pH monitoring for LPR results in over diagnosis and over treatment of the condition. Furthermore, they recommend PPI therapy should only be
utilized if the patient is also experiencing symptoms of GERD, and it should not exceed a treatment period of 2 months. They therefore dispute the efficacy of using PPI therapy for patients with symptoms of LPR alone. Finally they site the lack of randomized controlled trials supporting PPI therapy for LPR.

Belfasky et al created the Reflux Finding Score (RFS) and Reflux Symptom Index (RSI) to standardize both the laryngeal findings and symptoms of acid reflux in patients so outcomes in this area of research could be more accurately measured. The RFS is a severity scale with 8 items: subglottic edema; ventricular obliteration; erythema/hyperemia; vocal fold edema; diffuse laryngeal edema; posterior commissure hypertrophy; granuloma/granulation tissue; and thick endolaryngeal mucus. The possible score ranges from a minimum of 0 to a maximum of 26. A score of greater than 7 is 95% sensitive for LPR. The RSI is a self-administered 9-item severity scale for symptoms of LPR. Patients rank each of the nine symptoms on a scale from 0 to 5, 0 being “no problem” and 5 being a “severe problem”. The symptoms assessed include: hoarseness, throat clearing, post-nasal drip, dysphagia, breathing difficulties, chronic cough, lump in the throat, and heartburn. A score of greater than 13 is considered abnormal.

Two meta-analyses were completed in 2006 demonstrating that PPI therapy for LPR was no better than placebo. Qadeer et al evaluated data from 8 randomized controlled trials (RCTs) using either a primary outcome of 50% or greater reduction in LPR symptoms, or complete symptom resolution. Only one of the studies analyzed used a standardized tool to measure outcomes. This lack of standardization resulted in significant heterogeneity. Proton pump inhibitor therapy was once thought to have a low side effect profile but research is emerging demonstrating that it can lead to
infectious complications and nutritional deficiencies. It is imperative that clinicians determine the appropriate dosage and length of treatment required for LPR. The purpose of this review is to evaluate the latest placebo controlled RCT using the RFS and RSI to evaluate the efficacy of PPI therapy for LPR.

METHODS
An exhaustive literature search using the Medline, EBMRM, and CINAHL search engines was conducted from 2006-present with the following search terms: laryngopharyngeal reflux, proton pump inhibitors, extraesophageal, laryngitis, globus, throat clearing, and chronic cough. Randomized controlled trials comparing PPI to placebo for the treatment of LPR in adults were included. Trials were excluded if completed before 2006, or if they were previously evaluated in a meta-analysis. Studies written in foreign language and not translated were also excluded. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

RESULTS
A systematic literature review resulted in 102 potential articles for consideration. Five additional articles were obtained from the bibliography of UpToDate on the topic of LPR. After duplicates were removed 82 remained. Seventy-five were excluded based on review of title or abstract. There were 7 full text articles assessed for eligibility of which 4 were excluded because they did not use a control group for comparison, or measured an outcome other than LPR symptoms such as the amount of pepsin in the sputum. The remaining 3 articles met all inclusion and exclusion criteria (Table 1).
Lam et al 2010
This prospective, double-blind, randomized, placebo controlled study\(^{19}\) was conducted in China. A total of 82 participants were enrolled but only 40 were analyzed in each arm. The average age was 46.86 and 28\% were male. The patients were gathered from an outpatient otolaryngologist office and diagnosed with LPR via videostroboscopy. Participants were included if they met the following criteria; the presence of at least 1 of the following: hoarseness, globus, throat discomfort, and throat clearing for at least 1 month in the preceding 1 year; and endoscopic evidence of LPR with a RFS > 7 and absence of upper respiratory infection in the past 4 weeks or allergic causes of laryngitis. Participants were excluded if they were younger than 18, had an identifiable laryngeal pathology other than LPR, a history radiotherapy, gastroesophageal surgery, or if they were on acid suppressive therapy within the previous 4 weeks. Patients were randomized in a 1:1 fashion using computer-generated random numbers. The treatment group received rabeprazole 20mg twice daily for 12 weeks and implemented lifestyle modifications. Outcomes were measured using the RFS and RSI. There was no statistically significant difference in RFS between the treatment and placebo groups. There was statistically significant improvement between the treatment and placebo groups RSI at week 6 and week 12. This effect could no longer be demonstrated at week 18, which was 6 weeks after discontinuing the treatment. The authors conclude that patients with LPR require longer treatment duration with PPI. The funding for this research was provided by EISAI Company Limited the developers of rabeprazole.

Fass et al 2009
This prospective, double-blind, randomized, placebo controlled study\(^{23}\) was conducted in the United States. There were a total 41 participants and all were analyzed
as part of the data. Twenty-four patients were allocated to the treatment group and 17 to
the placebo group. The average age was 63.25 and 58% were male. The patients were
gathered from an outpatient otolaryngology clinic and diagnosed with LPR via
videostroboscopy. Participants were included in the study if they met any of the
following criteria, had posterior laryngitis in combination with: hoarseness, cough, throat
clearing, throat discomfort and globus; and GERD related laryngeal mucosal changes.
Participants were excluded if they were currently on anti-reflux treatment, had a history
of prior reflux or esophageal surgery, had been intubated in the preceding 3 months, had
been diagnosed with oropharyngeal or laryngeal cancer, were pregnant, or had an allergy
to PPI. They also excluded patients with any severe comorbidities. The authors provide
no information on how the randomization process was conducted. The treatment group
received esomeprazole 20mg twice daily for 12 weeks combined with implementing
lifestyle modifications. Outcomes were measured using the RFS, a daily voice use diary,
the Laryngopharyngeal Reflux Health-Related Quality of Life Questionnaire (LPR-
HRQL), the Short Form 36 (SF-36), and acoustic voice measurements. The study found
no statistically significant difference between the treatment group and placebo group for
any of the outcomes measured. They also found no difference in a subgroup analysis of
patients with abnormal esophagogastroduodenoscopy (EGD) findings at baseline. The
study was partially funded by Astra-Zeneca the makers of esomeprazole.

Reichel et al 2008
This prospective, double-blind, randomized, placebo controlled trial was
conducted in Germany. A total of 62 participants were enrolled and 58 were analyzed at
the studies completion. Thirty-one were allocated to the treatment group and 31 to the
placebo group. The average age was 48.7 and 51% were male. The patients were
gathered from an outpatient otolaryngologist office and diagnosed with LPR via videostroboscopy. Participants were included in the study if they had a RFS of greater than 7 and a RSI of greater than 13. Participants were excluded if they were younger than 18, had a history of laryngeal malignancy or gastrointestinal surgery, or if they had the need for continuous anticoagulation therapy with warfarin or aspirin. They were also excluded if they were treated with PPI or any other anti-reflux medication within the previous 3 months, were pregnant or lactating, had an allergy to a PPI, had a drug or alcohol addiction or any psychiatric disease. Patients were randomized in a 1:1 ratio, and the placebo pill was identical to the esomeprazole. The treatment group received esomeprazole 20mg twice daily for 12 weeks. No lifestyle modifications were implemented. Outcomes were measured using the RFS and RSI. The treatment and placebo groups demonstrated statistically significant improvement in the total RFS and RSI at week 6. There was no difference however, when the treatment group was compared to the placebo group. At 12 weeks the RSI of both study groups demonstrated improvement with a stronger effect in the treatment group. The study was funded by Astra-Zeneca the makers of esomeprazole.

**DISCUSSION**

The treatment of LPR with PPI therapy continues to be a highly controversial topic between the fields of otolaryngology and gastroenterology. The lack of adequate diagnostic testing and a proliferation of weak evidence for treatment leaves the practicing clinician with little guidance and their patients filled with frustration. Proton pump inhibitor therapy once thought to be an extremely safe treatment option, is now demonstrating complications related to respiratory infections, Clostridium difficile.
infections, and bone fractures with prolonged use. Two of the studies in this review demonstrate significant improvement in symptoms after 12 weeks of treatment. Reichel et al found patients improved the most in the symptom category of heartburn. Lam et al also noted the most improvement in heartburn, chest pain, indigestion, and excess throat mucus. These symptoms are characteristic of patients with classic GERD. Therefore, it appears, that patients with LPR and concomitant GERD symptoms, will achieve the greatest benefit from PPI therapy. It is important to consider other etiologies such as nonacid refluxate, sinusitis, vocal abuse, allergies, or other environmental agents if a patient’s symptoms do not respond to an initial 3-month trial of treatment. Shorter duration trials have been used to question the efficacy of PPI therapy but in the Reichel et al study the placebo effect that was seen at 6 weeks disappeared at 12 weeks. This raises the question as to whether or not it is appropriate to discontinue PPI therapy prematurely after a trial of only 2 months.

All three studies used the RFS to evaluate laryngeal finding outcomes. Only Reichel et al was able to demonstrate a statistically significant improvement in laryngeal findings after 12 weeks of treatment when compared to placebo. They found the greatest improvement in posterior commissure hypertrophy (P < 0.01). This is considered one of the most characteristic findings of LPR. Lam et al was unable to demonstrate a difference in laryngeal findings at 6, 12, or 18 weeks. When they compared baseline characteristics of the treatment group at 12 weeks the RFS was lower overall, specifically in vocal cord edema and laryngeal edema. Similar changes were found in the placebo group however, with decreased overall scores, and decreased vocal cord edema and laryngeal edema subgroup scores. Even at week 18, patients in the
placebo group continued to demonstrate improvement. The authors attribute lifestyle modifications to the ongoing decrease in RFS. The Fass et al study\textsuperscript{23} showed no improvement in total RFS after 12 weeks of treatment. They found no difference between the treatment group and the placebo group and no difference could be observed within the groups when compared to baseline.

Lam et al\textsuperscript{19} and Reichel et al\textsuperscript{24} utilized the RSI to measure symptom outcomes. Lam et al measured reduced total RSI scores at week 6 and 12. The most improvement between the groups was in breathing difficulties or choking episodes, troublesome or annoying cough, and globus. By week 18 a statistical difference could no longer be calculated. The authors believe this indicates PPI therapy for LPR requires treatment longer than 3 months. At 6 and 12 weeks when the treatment groups were compared to their baselines both studies demonstrated a statistically significant improvement in heartburn symptoms, but not throat symptoms. Fass et al\textsuperscript{23} used two health care quality of life questionnaires, the LPR-HRQL and the SF-36 combined with a voice use diary, and evaluated acoustic voice parameters to monitor improvement in symptoms. No statistically significant difference could be found at baseline, 6, or 12 weeks, between the treatment and control groups or within either group.

While the studies by Fass et al,\textsuperscript{23} Lam et al,\textsuperscript{19} and Reichel et al\textsuperscript{24} all provided important findings in the management of LPR with PPI therapy they also had limitations. All the studies had a small sample size. They were funded fully or in part by pharmaceutical companies. Publication bias seems less likely for Fass et al\textsuperscript{23} due to the lack of outcomes in their study. All studies chose to use 20mg twice daily as a dosing schedule. The current standard of care for LPR is 40mg twice daily.\textsuperscript{11} Reichel et al\textsuperscript{24}
chose 20mg because the typical practice for primary care providers in Germany is to start patients at a low dose. Fass et al used 20mg because there is no approved indication for 40mg PPI twice daily. The RFS\textsuperscript{1} can be subject to examiner bias; the Reichel et al study\textsuperscript{24} did not randomize their videostroboscopic exams and used only one blinded examiner for all patients. Therefore only the medication aspect of the study was double-blinded. The pharmaceutical company who funded the study was also involved in their randomization process further contributing to a publication bias. Ongoing research for LPR needs to have larger sample sizes, to study patients taking 40mg daily, and to follow patients for a minimum of 6 months. Diagnostic tests need to be refined so the inclusion criteria for research studies can be more objective.\textsuperscript{9,25,27}

**CONCLUSION**

The use of proton pump inhibitors for LPR continues to be a topic surrounded with controversy. The overall combined quality of the studies reviewed was low based on the GRADE criteria.\textsuperscript{21} The research supports a trial of twice daily PPI for at least 3 months if the patient is also experiencing symptoms of GERD.\textsuperscript{25} Patients with throat symptoms alone are unlikely to find relief from PPI therapy and should be evaluated for other possible etiologies such as non-acid reflux, allergies, sinusitis, environmental triggers, smoking, and vocal abuse.\textsuperscript{3} Until the medical community is able to develop a diagnostic test sensitive and specific enough to accurately detect LPR the inclusion criteria used in research will continue to dilute the findings.\textsuperscript{25,27} Further RCT that mirror the 40mg twice daily dosage used in clinical practice are needed, along with larger sample sizes, longer duration of study, and funding provided by an unbiased source.
REFERENCES


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**TABLE 1** Characteristics of Reviewed Studies, GRADE profile

- Lacked precision secondary to all data provided as P values as well as small sample sizes.
- Fass et al (23) placebo group had more males and were older than the treatment group. The placebo group also had more severe reflux symptoms and a higher # of acid reflux events and total acid exposure time than the treatment group.
- The RSI, LPR-HRQL, SF-36, and voice diary are all subject to recall bias. All the studies were funded fully or in part by pharmaceutical companies. Fass et al (23) demonstrates less likelihood of publication bias due to the lack of positive outcomes.