# Gastroesophageal Reflux Disease Associated With Anxiety: Efficacy and Safety of Fixed Dose Combination of Amitriptyline and Pantoprazole

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## Abstract

**Background:** The aim of the study was to evaluate the efficacy and tolerability of fixed dose combination of amitriptyline and pantoprazole in gastroesophageal reflux disease (GERD) associated with anxiety.

**Methods:** A non-randomized, open-labeled, non-comparative, multicenter study was conducted in a total of 99 patients (77 men and 22 women, mean age 44.16 ± 11.53 years). Each patient was administered a fixed dose combination of amitriptyline 10 mg and pantoprazole 40 mg once a day, for 4 weeks. GERD questionnaire, hospital anxiety and depression score (HADS) and SF-8 questionnaire (short-form health survey) were performed at baseline and at the end of study as assessment tools.

**Results:** At the end of study, data were extractable only in 96 patients because three patients were dropped out due to loss of follow-up at week 4. GERD symptoms and anxiety score reduced significantly (P < 0.0001) at week 4 compared to baseline. SF-8 score also improved significantly (P < 0.0001) at week 4. There were no adverse events reported.

**Conclusion:** Amitriptyline and pantoprazole combination was found to be effective and safe for management in GERD patients with co-existing anxiety.

**Keywords:** GERD; Anxiety; PPI partial responders; Amitriptyline; Pantoprazole

## Introduction

The prevalence of gastroesophageal reflux disease (GERD) has risen strikingly over the last few decades [1]. In 2011, a study reported 7.6% prevalence of GERD in India, whereas recently in January 2017, another study reported high prevalence of 39.2% [2, 3].

GERD is a condition characterized by the reflux of stomach contents into the esophagus, which causes several symptoms, such as heartburn and regurgitation. It is typically divided into three subtypes: reflux esophagitis (RE), non-erosive reflux disease (NERD) and Barrett's esophagus. GERD has been shown to have a significant negative impact on the quality of life (QoL) of affected patients and may even disrupt their daily activities [4].

For the management of GERD, physicians increasingly consider prescribing a (low- or standard-dose) once-a-day proton pump inhibitor (PPI) as first-line therapy [5]. However, the symptoms of GERD are sometimes impossible to control, and these patients tend to have a lower response rate, even to the most potent PPIs [6, 7]. Some studies have demonstrated that up to 40% of patients with heartburn reported either a partial or complete lack of response to PPIs taken once daily [8-10]. Failure of the PPI treatment to resolve GERD-related symptoms has become the most common presentation of GERD in patients seen by clinical gastroenterologists [11]. In a systematic review, El-Serag et al reported that persistent and troublesome GERD symptoms remained in 17-32% of primary care patients receiving PPI therapy and 45% of participants reported persistent GERD symptoms in observational primary care and community-based studies [12].

According to clinical data, psychological factors, including anxiety and depression, also develop in patients with GERD [4]. A study showed that the psychological scores for neuroticism, anxiety and depression were higher in patients with GERD than in healthy controls and were found to be positively correlated with symptoms of heartburn [13, 14]. A study evaluated the relationship between the efficacy of PPI therapy and health-related quality of life (HRQOL like physical health, mental health, sleep levels, anxiety levels, and depression levels) in GERD patients receiving PPI therapy and examined predictive factors affecting the response to PPI therapy. Study found that approximately 47% of GERD patients receiving PPI therapy were partial responders and that these patients had significantly more mental health, sleep, anxiety, and depression disorders in comparison to responders [15]. Moreover, in another study reported by Yang, anxiety and depression played an important role in the occurrence of GERD especially NERD with reduced QoL [4].

**Table 1.** Evaluation of GERD Using the GERD Questionnaire

| Parameters | Baseline | Week 4 | Mean difference (95% confidence interval) | Percent change (%) | P value |
|---|---|---|---|---|---|
| Heartburn | 2.823 ± 0.04682 | 0.9896 ± 0.02339 | -1.833 ± 0.05233 | 64.96 | < 0.0001 |
| Regurgitation | 2.156 ± 0.05984 | 0.125 ± 0.03393 | -2.031 ± 0.06879 | 94.20 | |
| Pain | 2.771 ± 0.04794 | 0.5 ± 0.05339 | -2.271 ± 0.07176 | 81.95 | |
| Nausea | 2.656 ± 0.05702 | 0.4167 ± 0.05058 | -2.24 ± 0.07623 | 84.31 | |
| Sleep disturbance | 2.365 ± 0.04938 | 0.4792 ± 0.05125 | -1.885 ± 0.07117 | 79.73 | |
| Additional medication | 2.719 ± 0.05278 | 0.4479 ± 0.05313 | -2.271 ± 0.07489 | 83.52 | |

Unpaired *t*-test

Based on the available evidences, this study was designed to establish the benefits of combining anti-anxiety (amitriptyline) with a PPI (pantoprazole) in GERD patients with coexisting anxiety.

## Materials and Methods

### Design and participants

This was a non-randomized, observational, multi-center study to determine the effectiveness and safety of the fixed dose combination of amitriptyline 10 mg and pantoprazole 40 mg once daily for 4 weeks.

A total of 99 GERD patients (men and women, mean age: 44.16 ± 11.53 years) reporting to Gastroenterology OPD, were screened for the intensity of heartburn, regurgitation, retrosternal pain, nausea, sleep disturbance and use of additional medication on four-point analog scale (0 - 3: 0 = none; 1 = mild; 2 = moderate and 3 = severe). Evaluation of anxiety symptoms was done using hospital anxiety and depression scale (HADS) which was a 7-item self-rating questionnaire. Respondents had to indicate the frequency of any symptom on a four-point scale. Scores were calculated as the sum of their respective 7-item scores (ranging from 0 to 21) where (0 - 7 = normal, 8 - 10 = borderline abnormal, 11 - 21 = abnormal) and short-form health survey (SF-8) questionnaire consisting of 8 items was done on six-point scale (1 - 6: 1 = very poor; 2 = poor; 3 = fair; 4 = good; 5 = very good; 6 = excellent).

### Inclusion and exclusion criteria

A total of 99 patients with GERD and anxiety symptoms who gave their consent in the vernacular language were included in the study. Eligible patients were in the age range of 25 - 80 years and were diagnosed to have GERD with coexisting anxiety by utilizing GERD and HADS questionnaire at the baseline.

The exclusion criteria included patients with any of the several conditions listed as follows: use of prescribed non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin; a history of upper gastrointestinal surgery; comorbidities, such as scleroderma, diabetes mellitus, autonomic or peripheral neuropathy, myopathy, functional bowel disorder or any un-

derlying disease (or medication) that might affect the lower esophageal sphincter pressure or increase the acid clearance time and inability or unwillingness to provide informed consent. Females who were pregnant or planning to conceive and lactating mothers were also excluded from the study.

## Results

### Evaluation of GERD using the GERD questionnaire

A total of 99 patients were included in the study but three patients were dropped out as they failed to report for the follow-up visit at week 4. The mean reduction in overall GERD symptoms was found to be clinically significant (P < 0.0001) at the end of the study (week 4) compared to baseline (Table 1).

### Evaluation of physical and mental health using SF-8 questionnaire

All parameters were found to be significantly (P < 0.0001) improved at week 4 compared to baseline. Increases in mean change of SF-8 questionnaire parameters from baseline to week 4 are presented in the Table 2.

### Anxiety score

The change in anxiety score was statistically significant (P < 0.0001) at week 4 compared to baseline (Fig. 1). The mean anxiety score in all participants was 20.98 ± 0.20412 at baseline and at the end of the study (week 4), it was significantly reduced to 7.01 ± 0.2292 with mean difference of -13.97 ± 0.03132 (95% confidence interval).

No patient reported any adverse effect at the end of the study.

## Discussion

The primary aim of this study was to establish the efficacy of low-dose amitriptyline with a conventional dose of PPI for the treatment of GERD with coexisting anxiety symptoms. We

**Table 2.** Evaluation of Physical and Mental Health Using SF-8 Questionnaire

| Parameters | Baseline | Week 4 | Mean change (95% confidence interval) | Percent change (%) | P value |
|---|---|---|---|---|---|
| General health | 3.969 ± 0.02319 | 4.948 ± 0.02718 | 0.9792 ± 0.03573 | 24.64 | < 0.0001 |
| Physical functioning | 4 ± 0 | 4.969 ± 0.01785 | 0.9688 ± 0.01785 | 24.20 | |
| Role physical | 3 ± 0 | 3.74 ± 0.05182 | 0.7396 ± 0.05182 | 24.66 | |
| Bodily pain | 3 ± 0 | 3.74 ± 0.04503 | 0.7396 ± 0.04503 | 24.66 | |
| Vitality | 3 ± 0 | 3.74 ± 0.04503 | 0.7396 ± 0.04503 | 24.66 | |
| Social functioning | 3 ± 0 | 3.74 ± 0.04503 | 0.7396 ± 0.04503 | 24.66 | |
| Role emotional | 3 ± 0 | 3.74 ± 0.04503 | 0.7396 ± 0.04503 | 24.66 | |
| Mental health | 3 ± 0 | 3.74 ± 0.04503 | 0.7396 ± 0.04503 | 24.66 | |

Unpaired *t*-test.

found favorable evidence for the efficacy of amitriptyline in improving anxiety symptom scores and physical and mental health in patients with GERD. In other words, we found that adding low-dose amitriptyline to a conventional dose of PPI resulted in significantly decreased symptoms, with no reported side effects. Interestingly, this outcome is very similar to the open-label response to low-dose amitriptyline with PPI seen with functional chest pain patients in 8-week duration [16].

In our study, we observed simultaneous reduction of both GERD symptoms and anxiety disorder. Typical symptoms of GERD like heartburn and regurgitation were found to be significantly reduced by 64.96% and 94.20%, respectively. Similarly improvement in anxiety score (66.58%) was also found to be significant from baseline. Along with that there was significant reduction in usage of additional medications like domperidone, levosulpiride and antacids by 83.52%. Evaluation of mental and physical health using SF-8 questionnaire also resulted in significant (P < 0.0001) difference from baseline with 24.64% in general health, 24.20% in physical functioning and 24.66% improvement in role physical, bodily pain, vitality, social functioning, role emotional and mental health. Tolerability of this combination was found to be excellent as no patients

reported any adverse effect.

In view of the fact that anxiety is highly prevalent 45.2% in reflux diseases like NERD compared to healthy patients [17], and may contribute to PPI failure, it is reasonable to prefer fixed dose combination of amitriptyline and pantoprazole in the management of GERD with coexisting anxiety.

The small sample size and short duration were the limitations of our study. Indeed, the short duration of most studies and the lack of follow-up after treatment cessation leave the question unanswered whether amitriptyline has long-term beneficial effects in GERD patients with anxiety symptoms, as well as the optimal treatment duration; thus study with large sample size and long duration is warranted. Nevertheless, this study is of value because it is the first study examining the efficacy of amitriptyline in patients of GERD with coexisting anxiety.

**Conclusion**

The fixed dose combination of amitriptyline and pantoprazole was effective in reducing GERD and anxiety symptoms,

# Mean change in Anxiety Symptom Score
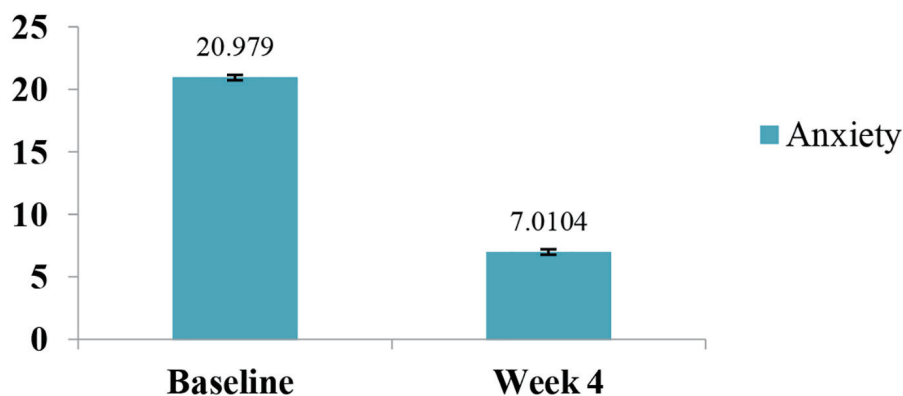


**Figure 1.** Mean change in anxiety symptom score.

without adverse events. The safety profile and efficacy in the subjects using amitriptyline as well as the significant improvement in physical and mental health scores may justify the addition of amitriptyline for the treatment of GERD with coexisting anxiety.

## Acknowledgments

## Conflict of Interest

None.

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