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Withdrawing PPI Therapy After Healing Esophagitis Does Not Worsen Symptoms or Cause Persistent Hypergastrinemia: Analysis of Dexlansoprazole MR Clinical Trial Data

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OBJECTIVES: **Withdrawal of proton pump inhibitors (PPIs) may induce symptoms in healthy volunteers, suggesting that discontinuing PPI therapy induces acid-peptic disease. Similar assessments in patients with documented acid-related disorders are lacking.**

METHODS: **We performed a retrospective analysis of data from 287 *Helicobacter pylori*-negative erosive esophagitis (EE) patients healed after 4 or 8 weeks of therapy with dexlansoprazole modified release (MR) or lansoprazole, and then randomized to placebo in 6-month maintenance trials. We compared serum gastrin levels and 24-h heartburn severity before enrollment in the healing trials (baseline) and after receiving placebo in the 6-month maintenance trials.**

RESULTS: **Mean gastrin values at maintenance months 1 and 3 were essentially unchanged (median changes, 1.0 and −1.0 pg/ml), showing that gastrin normalized within 1 month of discontinuing PPIs and remained flat. Mean heartburn severity at maintenance month 1 was <1 on a 5-point scale (1=mild) and significantly lower than at baseline (median decrease, 0.41 points; $P \leq 0.001$). Heartburn severity in patients healed at week 4 or 8 with either PPI was generally similar, suggesting that neither longer exposure nor more potent therapy was associated with rebound. In those with month 2 data, mean heartburn severity at months 1 and 2 was significantly lower than baseline (median decrease, 0.54 and 0.58 points; both $P<0.001$), indicating an ongoing symptom response for 2 months after PPI withdrawal.**

CONCLUSIONS: **In *H. pylori*-negative EE patients, there was no indication of recurring heartburn symptom worsening beyond baseline levels within 2 months of discontinuing 4–8 weeks of PPI therapy.**

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INTRODUCTION

Over the past two decades, proton pump inhibitor (PPI) therapy has been established as the standard of care for patients with gastroesophageal reflux disease (GERD) (1,2). Since the introduction of the prototype PPI omeprazole, researchers have hypothesized that elevated intragastric pH caused by blockage of proton pumps may stimulate compensatory mechanisms, leading to an increased capacity to stimulate gastric acid production after therapy is withdrawn (3–5).

The results of studies evaluating rebound acid hypersecretion (RAHS) following withdrawal of PPI therapy are conflicting. Hunfeld *et al.* (6) performed the first systematic review of the literature through October 2005 to investigate whether withdrawal of PPI therapy produced RAHS, defined as an increase in basal and/or stimulated gastric acid secretion above pretreatment levels following discontinuation of PPI therapy (7). The authors identified eight studies, six conducted in healthy volunteers and two in patients with acid-related disorders. Of the eight studies—including four double-blind, randomized studies—five did not provide any evidence of RAHS when PPI therapy was withdrawn, whereas three open-label studies suggested that RAHS may occur in *Helicobacter pylori*-negative patients after withdrawal of 8 weeks of PPI therapy.

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Based on their overall evaluation, the authors concluded that there was insufficient evidence of a clinically relevant increase in acid production after PPI withdrawal, primarily because of differences in study design, methodology, patient population, and contradictory results.

Since the Hunfeld review was published, data from two randomized, placebo-controlled trials conducted in healthy volunteers (8,9) have shown that withdrawal of short-term PPI therapy (4 or 8 weeks) seemed to induce acid-related symptoms. Based on their findings, the authors speculated that PPIs may aggravate symptoms in patients when therapy is withdrawn and that this symptom rebound may lead to PPI dependence. The potential to worsen symptoms in patients discontinued from PPI therapy is an important topic for clinical practice and warrants further investigation.

Dexlansoprazole modified release (MR) is a PPI that produces two distinct releases of drug and has been shown to significantly extend the duration of active plasma concentrations and the percentage of time pH >4 beyond that of conventional single-release PPIs (10–13). Because the degree of RAHS is thought to be correlated with the degree of acid suppression (14), dexlansoprazole MR is a good choice for further investigation. We performed a retrospective analysis of data from four phase III registration trials of dexlansoprazole MR (15–17) to determine whether patients with endoscopically confirmed erosive esophagitis (EE) receiving therapy with dexlansoprazole MR or lansoprazole developed RAHS and/or a worsening of symptoms when therapy was discontinued after healing.

METHODS

Patient population

We analyzed data from patients who participated in the pivotal studies for dexlansoprazole MR that evaluated healing of EE (15) and maintenance of EE healing (16,17). All trials were conducted in compliance with institutional review board/ethics committee regulations and within the ethical principles stated in the 1989 Declaration of Helsinki. All patients voluntarily signed informed consent forms in the region in which the patient was participating and completed any Health Insurance Portability and Accountability Act forms (US sites only) before any study-related procedure was initiated.

Patients were excluded if they were pregnant or lactating; tested *H. pylori* positive based on CLOtest (urease test; Kimberly-Clark, Roswell, GA), which is mandatory outside North America and performed in the United States and Canada for patients who tested positive by finger stick or serology at screening; had used prescription or nonprescription PPIs or histamine-2 receptor antagonists within 14 days of screening or throughout the study; had used nonsteroidal anti-inflammatory drugs chronically; had a history of active gastric or duodenal ulcers within 4 weeks of the first dose of study drug; or had acute upper gastrointestinal hemorrhage within 4 weeks of screening endoscopy. Previous use of PPIs (within 90 days of signing the informed consent form) was also recorded by patients enrolled in the trials.

Healing of EE was assessed in two identical double-blind, randomized controlled studies of 4,092 adult patients at 188 US and 118 non-US centers with endoscopically confirmed EE (ClinicalTrials.gov identifiers NCT00251693 and NCT00251719) (15). A total of 896 patients who were healed after 4 or 8 weeks of once-daily therapy with dexlansoprazole MR 60 or 90 mg or lansoprazole 30 mg were then enrolled into one of the two double-blind, placebo-controlled maintenance studies. In the Metz *et al.* (16) study, patients were randomized to dexlansoprazole MR 30 or 60 mg or placebo for up to 6 months (ClinicalTrials.gov identifier NCT00321737). The Howden *et al.* (17) study, which originally consisted of two identical study protocols (ClinicalTrial.gov identifiers NCT00255164 and NCT00255151), randomized patients to dexlansoprazole MR 60 or 90 mg or placebo for up to 6 months. Use of approved antacids, up to six tablets in a 24-h period, was permitted during healing and maintenance. Scheduled visits occurred at months 1, 3, and 6 in the maintenance studies. Patients whose healed EE relapsed at month 1 or 3 were discontinued from the studies. The majority of patients who relapsed at month 1 were in the placebo group, leading to a smaller number of placebo-treated patients at later visits.

Among patients who were healed after 4 or 8 weeks of treatment with dexlansoprazole MR or lansoprazole, 287 were subsequently randomized to placebo in the maintenance studies. The occurrence of RAHS was evaluated using available serum gastrin and symptom severity data from these patients. Within the placebo group, 24-h (daytime and nighttime) heartburn symptom severity was analyzed if data were available at baseline (before enrollment in the EE healing studies) and weeks 1, 2, 3, or 4, or months 1 or 2 of the maintenance studies. Heartburn symptom severity was assessed by daily diary. Patients rated heartburn severity using a 5-point scale where none (0) is no heartburn; mild (1) is occasional heartburn that could be ignored and did not influence daily routine or sleep; moderate (2) is heartburn that could not be ignored and/or occasionally influenced daily routine or sleep; severe (3) is heartburn that was present most of the day and/or regularly influenced daily routine or sleep; and very severe (4) is heartburn that was constant and/or markedly influenced daily routine or sleep.

Analyses

Evaluation of gastrin levels. Fasting serum gastrin levels were measured at baseline before EE healing treatment, at the end of EE healing treatment (day −1), and at the month 1 and month 3 visits in the maintenance studies. For these analyses, we also assessed the change from baseline to each of the post-baseline visits. RAHS was inferred if gastrin levels were increased above pretreatment levels following discontinuation of PPI therapy. An additional analysis was performed to look at patients defined by previous PPI usage to compare data for those who had reported taking a PPI within 90 days of signing an informed consent form with those who had not.

Symptom rebound evaluation. For each patient, mean severity of heartburn as assessed by daily diary was calculated and summarized for baseline (the 7-day period before randomization in the EE healing studies), during EE healing treatment, during

Table 1. Baseline demographics of placebo cohort[a]

Demographic variable	Placebo cohort (*N*=287)
Gender, n *(%)*	
Men	142 (49.5)
Women	145 (50.5)
Ethnicity, n *(%)*	
Hispanic/latino	35 (12.2)
Not hispanic/latino	252 (87.8)
Race, n *(%)*	
White	262 (91.3)
Black of African Heritage	15 (5.2)
Asian	5 (1.7)
Other	5 (1.7)
Age (years), n *(%)*	
<45	98 (34.1)
45 to <65	164 (57.1)
≥65	25 (8.7)
Mean±s.d.	48.9±12.90
Body mass index (kg/m²), n *(%)*	
<25	48 (16.7)
25 to <30	111 (38.7)
≥30	127 (44.3)
Unknown	1 (0.3)
Mean±s.d.	30.2±6.09

[a]Erosive esophagitis patients healed after 4–8 weeks of therapy with dexlansoprazole modified release (MR) or lansoprazole and then randomized to placebo in the maintenance of healing trials.

weeks 1, 2, 3, and 4 of maintenance treatment, during the first month of maintenance treatment, and for the change from baseline to each week and to the first month of maintenance treatment. Patients were considered to have sufficient diary data for the weekly summary of heartburn symptom severity if they had at least 4 days of evaluable diary entries within the given week, and sufficient diary data for the monthly summary if they had at least 15 days of entries. Two-sided Wilcoxon signed-rank tests were performed to test the change from baseline against no change. Symptom rebound was inferred as a worsening of symptoms after withdrawal of PPI therapy compared with baseline symptom assessments.

The analysis of 24-h heartburn severity was also performed in subgroups defined by previous PPI usage as reported by patients; healing treatment (dexlansoprazole MR compared with lansoprazole); duration of healing treatment (4 weeks compared with 8 weeks); and baseline body mass index (< or ≥30 kg/m²). In the subgroup of patients who also had heartburn severity results during the second month of maintenance treatment, a similar analysis was performed, which included two-sided Wilcoxon signed-rank tests for the change from baseline to month 2. In addition, we looked at mean heartburn symptom severity separately in the daytime and in the nighttime.

EE rebound. We also looked at the endoscopic grade of EE from the source documents of patients who relapsed after treatment with placebo in the maintenance studies. We compared these grades with the baseline EE grades of patients to see whether EE worsened after PPI therapy was withdrawn. For this analysis, 124 reports were available.

RESULTS

Baseline demographics for the cohort of patients (*N*=287) who were healed after 4–8 weeks of treatment with dexlansoprazole MR or lansoprazole and then randomized to placebo in the maintenance studies are shown in **Table 1**. Among the 287 patients, 5 were not included in the diary summary because of missing baseline diary. Of the other 282 patients, 60 were not included in the month 1 diary summary, including 48 who prematurely discontinued before day 30 and 12 additional patients who were in the maintenance study for at least 30 days but did not have sufficient diary data during the first 30 days. Of the 222 patients who were included in the month 1 diary summary, 125 patients were in the maintenance study for at least 30 days and the other 97 prematurely discontinued before day 30, but had sufficient diary data. Baseline median of mean heartburn symptom severity of the 222 patients included in the month 1 symptom analysis was 1.36. Of the 124 included in the EE rebound analysis, 31% had grade A esophagitis at baseline, 38% had grade B esophagitis, 27% had grade C esophagitis, and 4% had grade D esophagitis.

Gastrin evaluation

There was no evidence of RAHS as assessed by serum gastrin levels in this analysis. Among patients randomized to maintenance with placebo with available serum gastrin levels, mean (s.d.) gastrin level at baseline (pretreatment; *n*=216) was 59.9 (31.4) pg/ml. The changes from baseline to day −1 of maintenance trials (*n*=207), to maintenance month 1 (*n*=130), and to maintenance month 3 (*n*=52) were 85.5 (120.8) pg/ml, 3.5 (42.3) pg/ml, and 3.2 (66.8) pg/ml, respectively. As would be expected, gastrin values did increase from baseline to day −1 of the maintenance studies while patients were receiving active treatment (18,19). In patients randomized to placebo, mean gastrin values at months 1 and 3 were essentially unchanged from baseline. This indicates that gastrin levels normalized within 1 month of discontinuing PPIs and remained flat. Furthermore, data do not suggest any difference in the findings between those who used a PPI within 90 days of informed consent compared with those who did not (**Figure 1**).

Symptom rebound evaluation

There was no evidence of symptom rebound in this analysis. The mean 24-h heartburn severity was higher after PPI therapy was withdrawn compared with mean heartburn severity during PPI treatment, as would be expected. However, the mean heartburn severity at maintenance month 1, when gastrin values returned to

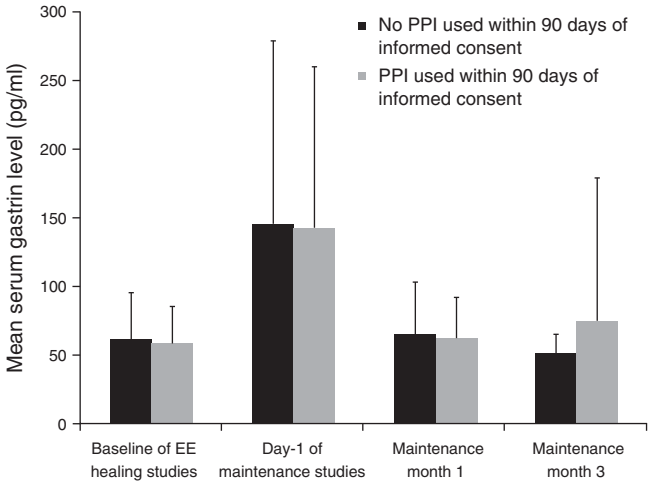

Figure 1. Mean serum gastrin levels. EE, erosive esophagitis; PPI, proton pump inhibitor. Error bars represent the s.d.

near-normal levels, was significantly lower than at baseline for all symptom analyses performed, despite the absence of PPI maintenance therapy (**Table 2**). When analyzed week by week during the first maintenance month, mean symptom severity scores remained flat—0.71, 0.93, 0.71, and 0.67 during weeks 1, 2, 3, and 4, respectively. **Figure 2** illustrates the median change in mean 24-h symptom severity scores from baseline to each week. During the first month of maintenance treatment, the median percentage of days with antacid use among placebo patients was 66%. In contrast, during the last 7 days before randomization in the EE healing study (baseline), the median number of days with antacid use among these patients was 6 days.

The median of mean heartburn severity was <1 (i.e., less than mild) for all analyses performed 1 month after discontinuing PPI therapy. Data do not suggest any difference in heartburn severity between those who reported using a PPI within 90 days of informed consent compared with those who did not (**Figure 3a**). Heartburn severity also appeared to be similar in patients healed with dexlansoprazole MR or lansoprazole (**Figure 3b**), with 4 or 8 weeks of healing treatment (**Figure 3c**), or in patients with body mass index of < or ≥30 kg/m^2 (data not shown). In addition, the changes in daytime heartburn severity and nighttime heartburn severity were consistent with that in 24-h heartburn severity (data not shown).

Because most placebo patients failed to maintain healed EE beyond month 1, there are fewer patients with data in the second month or beyond in the maintenance study. Among those with month 2 data, mean heartburn severity at months 1 and 2 was also significantly lower than at baseline (median decrease of 0.54 and 0.58 points; both $P<0.001$), indicating an ongoing symptom response for up to 2 months after PPI withdrawal.

EE rebound evaluation

More than half of patients whose EE recurred after maintenance therapy was discontinued relapsed to a less severe grade of EE compared with 18% who relapsed to a more severe grade of EE (**Table 3**).

DISCUSSION

RAHS and possible PPI dependency in patients discontinuing PPI therapy have been postulated to occur because of the hypertrophic effects of acid suppression, induced by increased gastrin levels, on histamine-releasing enterochromaffin-like cells (5,20). There was no evidence of RAHS in our analysis within 3 months of discontinuing 4–8 weeks of PPI therapy in a cohort of *H. pylori*-negative EE patients. Gastrin levels normalized within 1 month of discontinuing PPI therapy and remained flat at month 3. Furthermore, there was no evidence of symptom rebound within 2 months of PPI withdrawal. Rather, we observed a trend toward less severe, as opposed to more severe, heartburn after healing and PPI withdrawal—the opposite of symptom rebound. This is supported by the lower use of rescue medication during maintenance month 1 compared with baseline. Heartburn symptom severity after PPI withdrawal was similar among patients treated with dexlansoprazole MR or lansoprazole and for those treated for 4 or 8 weeks, suggesting that neither more potent therapy nor longer exposure was associated with rebound in the patients evaluated. These findings are based on data from well-controlled trials in an appropriate patient population and do not support the conjecture that withdrawal of short-term (i.e., <8 weeks) PPI therapy will produce symptomatic rebound that could lead to PPI dependency.

Data from our analysis contradict the findings of two recent trials that evaluated symptom development in healthy volunteers after withdrawal of a short course of PPI therapy (8,9). Reimer *et al.* (8) randomized subjects to receive either 8 weeks of esomeprazole 40 mg daily followed by 4 weeks of placebo or 12 weeks of placebo only. Symptoms were assessed weekly via questionnaires using a 15-item gastrointestinal symptom rating scale with a 7-point scale (1 = absence of bothersome symptoms; 7 = very bothersome symptoms). Mean fasting gastrin levels were also measured.

At least 1 symptom of heartburn, acid regurgitation, or dyspepsia was reported during weeks 9–12 by 44% (26/59) and 15% (9/59) of patients in the PPI and placebo groups, respectively ($P<0.001$). Mean scores for the subset of questions focusing on heartburn, acid regurgitation, and dyspepsia at baseline were 1.04 and 1.03 for the PPI and placebo groups, respectively, whereas scores for the last 4 weeks combined were 1.35 and 1.12, respectively ($P=0.001$) (8). Although this difference was statistically significant, scores were low in both and the numerical difference was modest (0.23 points). In addition, it cannot be determined if symptoms of this frequency and very mild severity would cause patients to resume PPI therapy. Plasma gastrin levels were significantly higher in the PPI group than the placebo group during treatment and correlated significantly with symptoms in the PPI group after therapy was discontinued (8). However, gastrin levels were within the normal range (<50 pmol/l) in both groups throughout the study and returned to baseline values by week 12 in the PPI group. There was an imbalance of *H. pylori*-positive subjects in the placebo group in this trial (13% vs. 2% in the esomeprazole group, $P=0.02$) (8).

Table 2. Change in mean severity of 24-h heartburn

Patients	Baseline of EE healing trials		During EE healing trials		Maintenance month 1		CFB to maintenance month 1	
	n	Median (Q1, Q3)	*n*	Median (Q1, Q3)	*n*	Median (Q1, Q3)	*n*	Median (Q1, Q3)
All patients with baseline and month 1 data	222	1.36 (0.86, 1.93)	221	0.14 (0.04, 0.50)	222	0.76 (0.37, 1.38)	222	−0.41[a] (−0.94, −0.02)
No PPI used with 90 days of informed consent	127	1.36 (0.86, 2.00)	126	0.15 (0.04, 0.48)	127	0.75 (0.37, 1.29)	127	−0.43[a] (−0.98, 0.01)
PPI used with 90 days of informed consent	95	1.36 (0.79, 1.93)	95	0.13 (0.04, 0.52)	95	0.77 (0.37, 1.45)	95	−0.35[a] (−0.82, −0.09)
Healed on dexlansoprazole MR	151	1.50 (0.86, 2.00)	150	0.15 (0.05, 0.52)	151	0.85 (0.35, 1.45)	151	−0.40[a] (−0.97, −0.07)
Healed on lansoprazole	71	1.21 (0.64, 1.79)	71	0.12 (0.02, 0.38)	71	0.70 (0.38, 1.11)	71	−0.43[a] (−0.90, 0.00)
Healed at week 4	187	1.43 (0.80, 2.00)	186	0.15 (0.04, 0.50)	187	0.82 (0.38, 1.43)	187	−0.35[a] (−0.93, −0.03)
Healed at week 8	34	1.18 (0.86, 1.64)	34	0.09 (0.04, 0.34)	34	0.58 (0.35, 1.03)	34	−0.58[a] (−1.13, 0.08)

EE, erosive esophagitis; CFB, change from baseline; MR, modified release; PPI, proton pump inhibitor.
[a]$P \leq 0.001$ from a two-sided Wilcoxon signed-rank test.
Mean severity is calculated for each patient based on a 5-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.

Because *H. pylori*-positive subjects are generally less likely to experience rebound problems (14), and because the numerical differences between groups was quite small, it is possible that *H. pylori* status had an impact on the findings in this study population. Furthermore, because symptoms were only evaluated weekly, there may have been the possibility of recall bias.

Niklasson *et al.* (9) enrolled *H. pylori*-negative subjects in a randomized, double-blind, placebo-controlled trial evaluating dyspeptic symptoms after discontinuation of PPI therapy. A total of 48 female volunteers reported their symptoms daily throughout a 2-week run-in period, during the 4 weeks of treatment with either pantoprazole 40 mg daily or placebo, and for 6 weeks after treatment was discontinued (9). Symptoms were evaluated daily using a modified Swedish version of the Glasgow dyspepsia score questionnaire, which was designed to reflect on symptom severity, nocturnal disturbance, and behavioral response to sustained symptoms, and were scored on a scale of 0 (no symptoms) to 12 (9). Fasting and meal-stimulated gastrin levels were measured the day before treatment was started, on the last day of treatment, and then 6 weeks after treatment was discontinued (9).

During the first week after treatment was discontinued, 44% (11/25) and 9% (2/23) of subjects in the pantoprazole and placebo groups, respectively, reported dyspeptic symptoms ($P = 0.009$) (9). The difference between the groups was also significant during the second week, but not during the remaining 4 weeks. Mean symptom scores at baseline were 0.54±1.3 and 0.20±0.7 in the pantoprazole and placebo groups, respectively, and 5.7±11.7 and 0.74±2.6 ($P < 0.01$), respectively, 1 week after treatment discontinuation (9). Although symptom scores decreased in the second week post-treatment, they were still significantly different between the two treatment groups ($P < 0.05$), but this significance disappeared in weeks 3–6. Symptoms resolved quickly; the median symptom duration was 4 days in the subgroup of PPI-treated subjects who experienced symptoms (9). Mean fasting and meal-induced serum gastrin levels were significantly higher in the pantoprazole group than in the placebo group during the last week of treatment and were significantly correlated with symptom scores ($P < 0.01$) (9). There was no significant difference between groups at 6 weeks after treatment was discontinued. Because the first measurement of gastrin scores was not until 6 weeks after treatment was discontinued, it is possible that the difference between groups resolved before gastrin levels were assessed post-treatment (9).

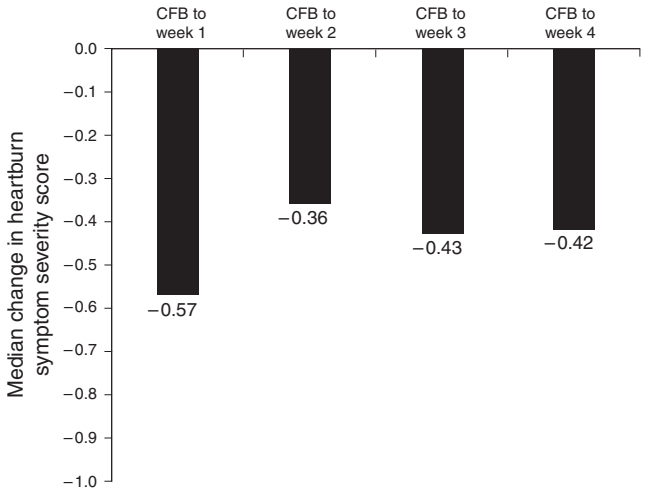

Figure 2. Median change from baseline in mean 24-h heartburn symptom severity in all placebo-treated patients with data for baseline and weeks 1–4 of the maintenance studies. CFB, change from baseline. $P < 0.001$ for comparison of change from baseline with no change for each week; Wilcoxon signed-rank test.

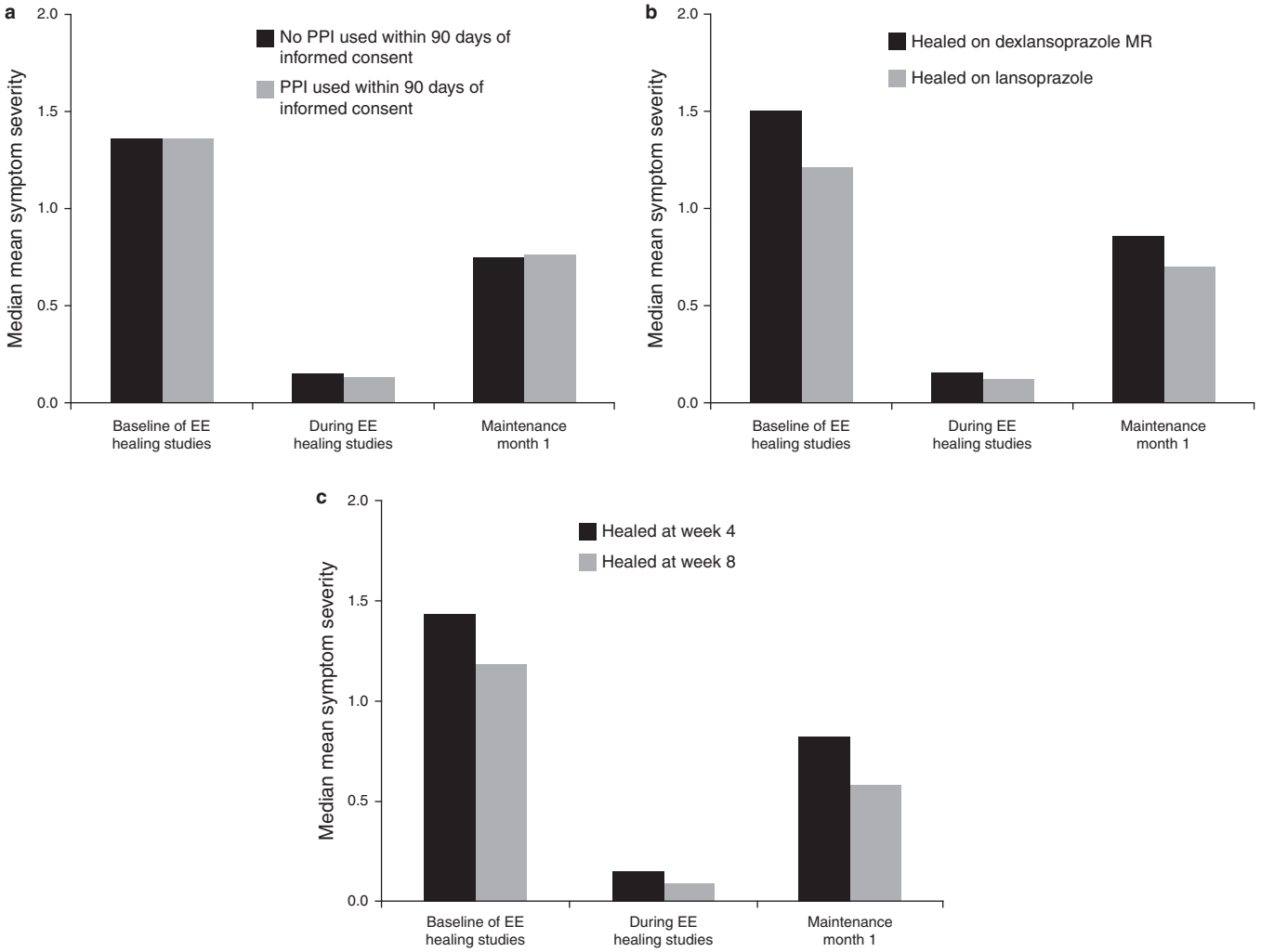

Figure 3. Heartburn severity during follow-up. Mean 24-h heartburn severity (median) in all placebo-treated patients with baseline and month 1 data shown by (**a**) previous PPI usage, (**b**) healing therapy, and (**c**) duration of healing therapy. EE, erosive esophagitis; PPI, proton pump inhibitor. Mean severity is calculated for each patient based on a 5-point scale: 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe.

Table 3. Change in Los Angeles grade of erosive esophagitis

Start of healing study (baseline) Grade, n	Relapse to grade A *n*	Relapse to grade B *n*	Relapse to grade C *n*	Relapse to grade D *n*
Grade A=39	23	14	2	0
Grade B=47	21	20	6	0
Grade C=33	3	17	13	0
Grade D=5	0	0	2	3

Both normal volunteer studies cited in this paper utilized a broader acid peptic symptom complex when defining rebound, including regurgitation and dyspepsia. Our definition of symptom rebound, which was defined as the recurrence of heartburn symptoms of greater severity than reported at baseline, has been utilized in several previously published clinical trials of GERD treatment. Although we cannot exclude that earlier onset of symptom relapse, rather than increased severity, could reflect rebound, timing of relapse rates reported in our study was similar to that reported in other placebo-controlled studies. Overall, it is difficult to say whether the conclusions from either normal volunteer trial (8,9) are clinically relevant and can be extrapolated to patients

who are receiving therapy with PPIs to treat acid-related disorders. The fact that healthy volunteers receiving placebo reported symptoms in both trials may be an indication that subjects in these trials were sensitized to report symptoms. It is also possible that the PPI-treated subjects were reporting side effects of therapy rather than symptoms of GERD. The fact that some, but not all, subjects receiving PPIs reported symptoms, and that these symptoms were generally mild and transient, tends to support this hypothesis.

In one double-blind, randomized, placebo-controlled study, Farup *et al.* (21) evaluated symptoms after PPI withdrawal in a population of GERD patients. In this crossover trial, 62 patients were treated with high doses of lansoprazole (60 mg daily) followed by placebo, or vice versa, to see if PPIs would aggravate symptoms after withdrawal of 5 days of therapy (21). The authors chose this treatment period because a short course of PPI therapy is often used as a confirmatory test in patients suspected of having an acid-related disorder. In this trial, symptoms at 12–14 days before and after the treatment period were generally similar between the two treatment groups. There was no indication of symptom rebound (21).

Our analysis does have some limitations. It is difficult to distinguish symptom rebound from symptom recurrence in patients suffering from a chronic, relapsing disorder. We inferred symptom rebound based on a worsening of symptoms when therapy was withdrawn beyond severity recorded at baseline. This definition does test the hypotheses that withdrawal of PPI therapy may somehow aggravate symptoms in patients with an acid-related disorder.

Furthermore, the EE healing studies preceding the maintenance studies only included active PPI treatment groups (dexlansoprazole MR or lansoprazole) and did not have a placebo group, which could have yielded additional interesting findings. We also used serum gastrin levels as an indirect measure of acid secretion, which can be determined more directly by several methods, including aspiration. Measuring area under the plasma concentration time curve after a meal would also provide a better surrogate than fasting serum gastrin. These more direct assessments of gastric acid levels were not performed in the original studies; as such, they were not available for this secondary analysis.

Regarding the observation that grades of EE tended to be less severe in the maintenance period than at baseline, we cannot completely exclude a potential effect from regression to the mean. However, any potential effect from regression to the mean would have been indirect because of the previous EE healing studies. The effect could only have contributed to the healing and/or improvement during the EE healing studies, but not the change during the EE maintenance studies. Finally, we only had data available for patients who were treated with PPIs for 4 or 8 weeks before being discontinued from therapy. Although our analysis clearly showed no evidence of acid or symptom rebound that could provoke PPI dependence, we cannot infer the effect of withdrawing patients from long-term PPI therapy based on data from a short-term analysis.

The recent studies in healthy volunteers (8,9) certainly renewed interest in the study of RAHS and will contribute to the ongoing debate regarding the occurrence and clinical significance of RAHS. Likewise, the data from our analysis in symptomatic EE patients will contribute to this debate. However, pending consistent and compelling data that withdrawal of PPIs produces acid or symptom rebound in patients that results in PPI dependence, we see no reason for clinicians to alter their prescribing habits.

We would recommend that physicians continue to follow the evidence-based AGA (American Gastroenterological Association) 2008 guidelines (1), which state that empirical therapy with PPIs is considered appropriate to initiate therapy in patients with uncomplicated heartburn. Maintenance therapy is appropriate in patients with EE. Additionally, the majority of patients with GERD symptoms severe enough to warrant initial PPI therapy will require long-term PPI therapy to achieve adequate symptom control. In these patients, the dose should be titrated to the lowest effective dose that achieves symptom control.

Currently, the majority of total PPI prescriptions are for long-term therapy (variably defined as one prescription repeated over 12 months to continuous therapy that ranges from 4 to >12 months) (22). Although PPIs are often prescribed for long-term usage, patient adherence to PPI regimens appears to be suboptimal. Van Soest *et al.* (23) evaluated PPI usage among 386,002 patients for a mean of 3.4±2.4 years and found that only 22% of the study cohort continued PPI treatment for at least a year. Adherence was low to moderate in more than half of all patients, reflecting a high prevalence of intermittent therapy among PPI users, which may be problematic for some patients. Therefore, it is also important for clinicians to regularly monitor the status of patients on PPI therapy to ensure that they are receiving optimal treatment.

In summary, the findings of our analysis show that discontinuation of 4 or 8 weeks of PPI therapy did not produce any evidence of relapse of heartburn symptom severity to levels worse than pretreatment levels in a patient population that derived benefits from PPI therapy. Furthermore, serum gastrin levels were shown to normalize within a month of discontinuing therapy and symptoms appeared to be less severe as opposed to more severe when PPI therapy was withdrawn. Clearly, there was no indication that discontinuation of a 4- or 8-week course of PPI therapy is causing PPI dependency. However, the current findings do not exclude the possibility of RAHS following discontinuation of long-term PPI therapy.

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CONFLICT OF INTEREST

Guarantor of the article: David C. Metz, MD.

Specific author contributions: Initiated the study concept and design, analysis, and interpretation of data, critical revision of the paper: David C. Metz; study design, analysis, and interpretation of data; critical revision of the paper: Betsy L. Pilmer; study design, conducted the data analysis, and critical revision of the paper: Cong Han; study design, analysis and interpretation; critical revision of the paper: M. Claudia Perez. All authors have seen and approved the final report.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Healthy volunteers seemed to experience acid-related symptoms after withdrawal of a 4- or 8-week course of proton pump inhibitor (PPI) therapy.
- ✓ Data are needed to assess whether patients who discontinue PPI therapy experience worsening symptoms that may lead to PPI dependency.

WHAT IS NEW HERE

- ✓ Symptomatic erosive esophagitis patients treated with PPIs for 4 or 8 weeks did not experience a worsening of heartburn symptoms beyond pretreatment levels when therapy was withdrawn after healing.
- ✓ There was no evidence that PPI therapy aggravates the underlying disorder.

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