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Review Article

Efficacy and Safety of Omeprazole for the Treatment of Acid Peptic Disorders: A Systematic Review and Meta-Analysis

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Background Aim. To compare the efficacy of omeprazole to other proton-pump inhibitors (PPIs) or placebo for the treatment of acid peptic disorders (APDs) using a comprehensive literature search including hard-to-access journals and non-English articles. *Methods*. PubMed, Google Scholar, and China National Knowledge Infrastructure were searched (from inception to March 2023) for trials comparing omeprazole to other types of PPIs or placebo for the treatment APD. Efficacy was analyzed separately for erosive diseases and nonerosive diseases. Primary outcomes included improvement of APD symptoms and frequency of ulcer or erosion healing. Secondary outcomes included adverse events, cost effectiveness, nocturnal acid breakthrough, and length of stay if hospitalized. Random and fixed-effects models were used to determine estimates of efficacy. *Results*. Thirty-one eligible trials ($N = 10{,}539$ participants) were analyzed, including 12 articles not typically included in previous reviews due to translation or journal access issues. Omeprazole significantly improved heartburn compared to placebo (RR = 2.47, 95% CI: 2.13 and 2.86, and $p < 0.001$) and was equivalent to the other five types of PPI. Omeprazole had significantly fewer patients reporting adverse events versus placebo (11% versus 31%, respectively) and other PPIs. Omeprazole was the most cost-effective PPI compared to the other types of PPIs in India. *Conclusions*. Omeprazole continues to be an effective proton-pump inhibitor to treat patients with acid peptic disorders and was well tolerated. Omeprazole was significantly better than placebo and was equivalent with other PPIs for curing heartburn and was equivalent to other PPIs for the healing of ulcers or erosions in addition to being the most cost-effective.

1. Introduction

Acid peptic disorders (APDs) continue to be a common disorder seen by primary care physicians and gastroenterologists and place a heavy burden on healthcare systems [1]. In 2019, 309,381,599 cases were reported in a survey of 206 countries [2]. APD includes gastroesophageal reflux disease (GERD) and erosive ulcers (including gastric, duodenal, and esophageal). GERD is classified into the following three categories: (1) nonerosive reflux disease (NERD), (2) erosive esophagitis (EO), and (3) Barrett's esophagitis. The worldwide prevalence of GERD ranges from 7% to 52%, ranges from 8 to 30% in India, and has a high impact on the quality of life [2–8]. NERD is more common (~70%) and 10–30% have EO [6]. The prevalence of duodenal ulcers also varies greatly in different countries as follows: 2.1% in Sweden, 3% in India, 3.9% in Italy, 5.6% in Northern Saudi Arabia, 7.4% in Bangladesh, and 13.3% in China [9, 10].

Standard treatments for APD include the use of PPIs, adjunctive treatments (histamine H2 receptor antagonists, prokinetics, and alginate), surgery, life-style changes, and dietary considerations [1, 11, 12]. The World Gastroenterology Organization, Chinese, Korean, and Japanese guidelines recommend the first line of treatment to be a PPI given over 4–6 weeks, but there is no consensus of which type of PPI is more effective [1, 13–20]. PPIs differ in their pKa, bioavailability, peak plasma levels, route of excretion, recommended doses, and level of efficacy [9, 21]. The choice of which individual PPI drug is more effective and safe is still controversial. In addition, whether the efficacy of PPIs differs for the different APD syndromes is rarely directly compared.

Our aim in this study is to identify and analyze data from randomized, controlled trials (RCTs) to determine efficacy and safety for the most commonly used PPI (omeprazole) compared to the other types of PPIs or placebo and to determine the efficacy separately for NERD, EO, and erosive ulcers.

2. Methods

2.1. Protocol and Registration. The project and protocol for this meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [22]. The PRISMA checklist is provided in Supporting Information Table 1. The project and protocol were prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD 415397 (April 7, 2023), https://www.crd.york.ac.uk/PROSPERO/).

2.2. Search Strategy. PubMed, Google Scholar, and the China National Knowledge Infrastructure (CNKI) databases were searched (from database inception to March 30, 2023) to identify prospective RCTs or cross-over trials comparing omeprazole to other types of PPIs or placebo. The search strategy for PubMed was: ((((GERD) AND (omeprazole) AND (randomized controlled trial OR cross-over) AND (efficacy) AND NOT (prokinetics) OR NOT (alginate)))). Secondary searches of grey literature included reference lists, authors, reviews, meeting abstracts websites, and https://clinicaltrials.gov for unpublished trials. There were no language restrictions and articles in languages other than English were translated and reviewed.

2.3. Study Selection. Inclusion criteria included randomized, controlled clinical trials (RCTs) with prospective parallel groups or cross-over design with a minimum of two weeks washout period in children or adult subjects with diagnosis of acid/peptic disorder including either GERD, NERD, OE, upper gastrointestinal (GI) ulcers, GI bleeding, and presence or absence of *H. pylori*. Included interventions are as follows: omeprazole (oral or IV) for at least 4 weeks (later amended to at least one week) compared to other types of PPIs (esomeprazole (ESO), ilaprazole (ILA), lansoprazole (LAN), pantoprazole (PAN), rabeprazole (RAB), or placebo). Study outcome includes a measure of improvement of APD symptoms and/or ulcer/erosion healing.

Exclusion criteria included nonhuman studies, case reports or case series, early phase 1 (safety) or 2 (mechanism of action, dose ranging, formulation, kinetics) studies, validation of measurement tools for APD, no control group, intervention not well-described, no relevant outcomes provided, not a comparison of interest, reviews, meta-analysis, duplicate reports, presence of other disorders with similar symptoms (organic, metabolic, or drug-induced, chronic cough or asthma, simple laryngitis, Zollinger–Ellison syndrome, primary motility disorder, esophageal stricture, Barrett's esophagus, upper GI malignancy or other severe comorbidity), PPI treatment less than 1 week, only non-PPI comparison group (prokinetics, H2 receptor antagonists, surgery, alginates, or potassium-competitive acid blockers), or did not contain original quantitative data.

2.4. Data Extraction. Two reviewers (LV and PM) independently screened titles and abstracts of studies identified by the search strategies. Data from all full-text articles were extracted and reviewed independently by two reviewers using a predesigned data extraction form following the standard methods for systematic reviews and meta-analysis [22, 23]. Any disagreements were discussed until resolved.

The data extracted included PICO data: (1) population (age range and country), (2) intervention (type of PPI or controls used, daily doses, formulation, duration, and follow-up times), (3) comparisons (type of control group either placebo or open and unblinded), (4) outcomes, including improvement in APD symptoms, improvement in symptoms scores (frequency scale for symptoms of GERD (FSSG), dyspepsia symptom scores, heartburn scores, symptom index, etc.) and/or ulcer or erosion healing rates, time to ulcer healing, pH > 4 for 24 hours by treatment end, or percent remaining in remission.

2.5. Primary Outcomes

2.5.1. Improvement in APD Symptoms for NERD. This outcome was measured as either "overall improvement/cure" and by improvement of specific APD symptoms (heartburn, pain, and nausea). Other potential outcome measures included frequency remaining in remission, pH > 4 for 24 hours at the end of the treatment period, prepost improvement of esophageal pH, improvements in symptom scores (dyspepsia or heartburn and composite laryngeal score), or other visual analogue scales for symptom severity.

2.5.2. Frequency of Ulcer/Erosion Healing for Erosive Disease (DU/PU or EO). Erosion/ulcer healing has been defined as epithelium or mucosa healed, no ulcer crater by end of treatment, scarring only, presence or absence of inflammation, ulcer size reduced by >50%, or "total effective rate" (which includes frequency of completely healed (with

or without inflammation) and ulcer size reduced >50%) but does not include ulcers or erosions that were only improved or had no changes.

2.6. Secondary Outcomes. Data were collected on safety (adverse events), cost-effectiveness, nocturnal acid breakthrough, and length of hospitalization. Cost-effectiveness comparing the direct cost of omeprazole treatment versus the cost of other types of PPIs will be determined. Direct costs of treatment for patients with ulcers or erosions were calculated based on the cost per dose of PPIs available in India (from available website of medications (https://www.1mg.com/drugs/)), standard doses for each PPI recommended from current guidelines [16], costs/duration of standard treatment (4 weeks)/PPI, and costs associated with patients who did not respond to the initial 4 weeks requiring additional 4 week treatment (percent failure rate based on the mean failure rate for each PPI and standard dose from included trials). Total direct costs of treatment were defined as cost per PPI type for initial 4 weeks plus subset requiring additional therapy/100 patients. Indirect costs were not calculated due to the paucity of indirect data in the included trials.

2.7. Study Quality. Each included RCT was reviewed for quality and risk of bias and scored independently by both coauthors using standard methods [24]. The risk of bias (RoB) was assessed with the RoB 2.0 tool and was graded (high, low, or some concerns) for each of the five types of bias (randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of the reported result) [24]. Disagreements were resolved by discussion between reviewers or consultation with a third reviewer if necessary. A summary table of risk of bias was generated and the effect of study quality was assessed in trials with a low risk of bias [25].

2.8. Statistical Analysis. Inclusion of studies in meta-analysis required at least two RCTs or cross-over trials using a common outcome measure by the type of control (placebo or same type of PPI). Statistical analysis and generation of forest plots of pooled summary estimates was performed using Stata software version 16 (Stata Corporation, College Station, Texas) with meta-analysis modules [26]. Bayesian random effects models were used for the meta-analyses if significant heterogeneity was detected (overall $I^2 \geq 50\%$); otherwise, fixed-effect models were used [27]. Dichotomous outcomes were assessed using relative risks (RRs) and 95% confidence intervals (CI) and continuous outcomes were assessed using standardized mean difference (SMD) and 95% CI using standard methods [28]. Outcomes were analyzed separately by the type of APD as follows: nonerosive syndrome (NERD) or erosive syndrome (EO or ulcers). The significance level was set at p value ≤ 0.05. Heterogeneity across trials was evaluated using the I^2 statistic [26]. To assess sources of heterogeneity or inconsistencies and their influence on efficacy, the following data on potential confounding factors were collected: study design (double blinded or open), study quality, setting (inpatient or outpatient), and *H. pylori* status. For data missing from the published article, we attempted to contact the author. Publication bias was assessed using funnel plots and Egger's test [26]. Subgroup analysis was used to explore sources of heterogeneity (geographic region, PPI dose, length of PPI treatment, and study quality), and assessed with the Cochrane Q test (X^2 test statistic) [28]. Sequential sensitivity analysis was done to explore the extent outcomes were dependent upon a particular trial, but none were found.

3. Results

3.1. Literature Search. The literature search resulted in 615 articles that were screened and 584 were excluded (Figure 1). Thirty-eight trials were included in the qualitative analysis but seven were excluded (Supporting Information Table 2) [29–35]. A total of 31 RCTs were included in our review (10,539 participants) with 41 separate treatment arms [36–66]. The literature search found 12 articles not included in previous reviews due to translation or journal access issues. Eleven trials were translated from the original Chinese language [43, 44, 48, 50, 51, 54, 61–64, 66] and one from the original French [55]; all others were in English.

3.2. Study Participant Characteristics. The characteristics of the trials and study participants are provided in Table 1. All trials were conducted in adults (range: 16–85 years old). Patients had erosive ulcers ($n = 19$, 61%) or NERD ($n = 7$, 23%), and only five (16%) were in patients with EO. Most trials did not describe if the patients were outpatients or inpatients ($n = 22$, 71%), seven trials (23%) were done in outpatients, and two trials enrolled both inpatients and outpatients.

3.3. Study Design. The study size ranged widely from 19 to 2,645 enrolled patients per trial (mean: 350 ± 549). The geographic region where the trial was conducted was varied as follows: Asia (52%), Europe (32%), USA, (6%) or mixed countries (10%). Most of the trials were double-blinded ($n = 15$, 48%), 14 (45%) were open trials, and two (7%) were single blinded. Attrition or lost to follow-up (Table 1) was not reported in 11 trials (36%) and ranged from 0 to 32% in trials with attrition data. Most trials ($n = 19$, 61%) reported low (ranging from 0 to 25%) attrition rates and one trial reported higher attrition (32%) [47].

3.4. Characteristics of the Interventions. Of the 31 RCTs, omeprazole was compared to placebo ($n = 6$, 19%), or esomeprazole ($n = 2$, 7%), or ilaprazole ($n = 4$, 13%), or lansoprazole ($n = 6$, 19%), or pantoprazole ($n = 10$, 32%), or rabeprazole ($n = 3$, 10%). Typically, omeprazole was given at a dose of 20 mg/d (33 treatment arms) but was also given at 10–40 mg/d (8 arms), Table 1. The most common duration for omeprazole was for 4 weeks (32 arms) but ranged from 10 days to 8 weeks. In one trial, omeprazole was given for 4 weeks for duodenal ulcers or 6 weeks for gastric ulcers [61].

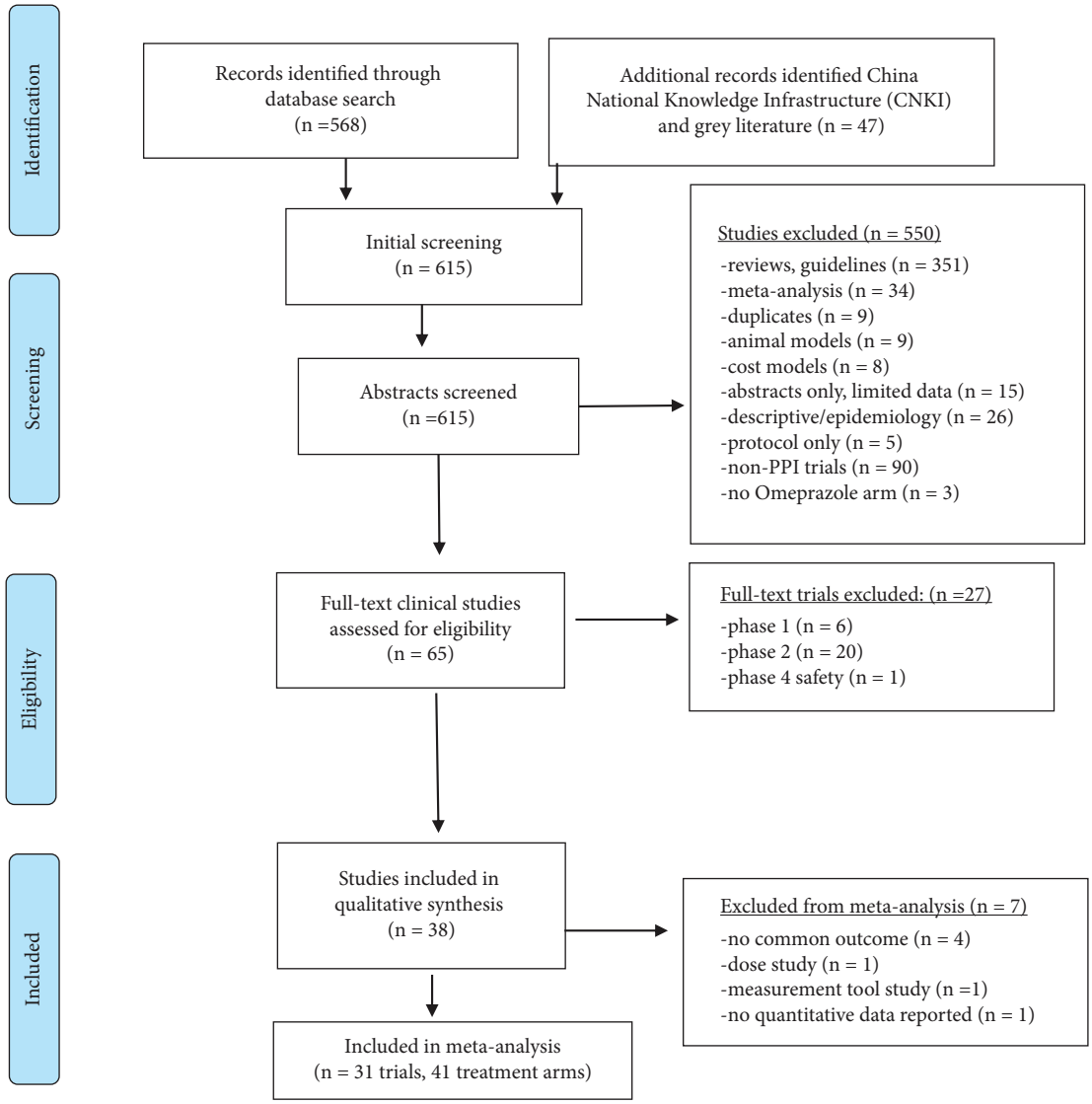


Figure 1: PRISMA flowchart of literature search.

Most trials did not follow patients after the PPI study was stopped ($n = 25$, 81%), but six trials did follow patients for varied durations after the study PPI was discontinued as follows: 2–6 weeks [46, 53], or 6 months [39, 40, 64], or 18 months [41].

3.5. Efficacy of Primary Outcomes. The most consistently reported outcome for improved APD symptoms was for heartburn relief. Improvements of other specific symptoms (nausea, regurgitation, belching, bloating, and pain) did not have sufficient numbers of trials within PPI control groups to be analyzed. Only one trial reported the frequency of ulcer remissions [41] and only one trial reported pH levels over 24 hours during the trial [52].

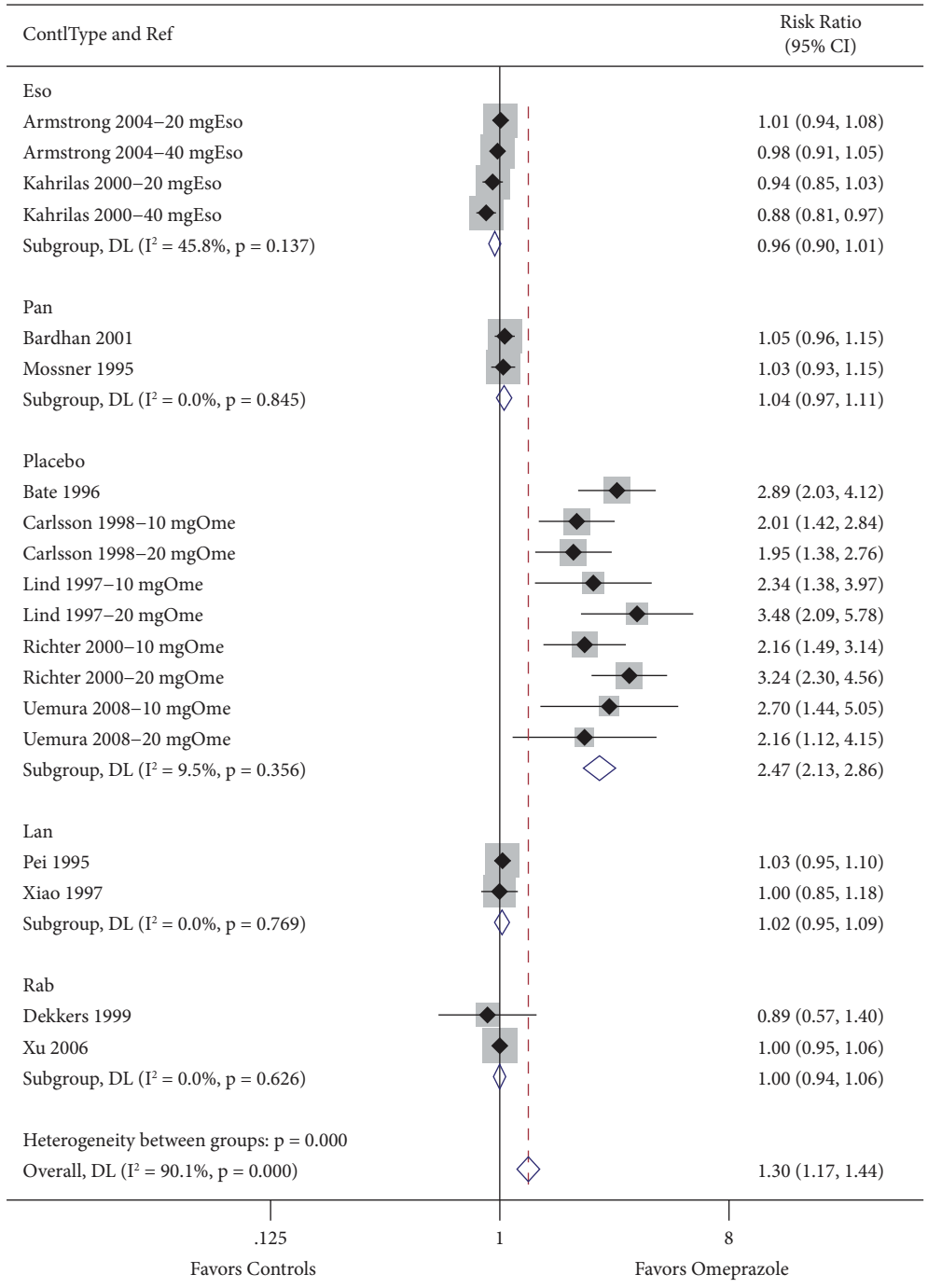
3.5.1. Heartburn Relief. Efficacy for heartburn was assessed in 6 trials (11 arms) in patients with NERD, 4 trials (5 arms) in patients with EO, and 5 trials (5 arms) in patients with ulcers (Supporting Information Table 3). Significant publication bias was found, Egger's test = 4.99, and $p < 0.001$ (Supporting Information Figure 1) due to studies comparing omeprazole and placebo, which were all strongly positive. Our meta-analysis using a random effects model of omeprazole compared to placebo or other PPIs revealed found efficacy significantly varied by the type of control ($X^2 = 91.07$, $p < 0.001$). Omeprazole significantly reduced heartburn by 2.5 times compared to placebo (RR = 2.47, $p < 0.001$), as shown in Figure 2. The efficacy of omeprazole to reduce heartburn was equivalent to the other three types of PPI (Figure 2): pantoprazole (RR = 1.04, $p = 0.26$), lansoprazole (RR = 1.02, $p = 0.51$), and rabeprazole (RR = 1.0, $p = 0.62$). Omeprazole was slightly less effective than esomeprazole (RR = 0.95, $p = 0.02$) for heartburn relief. As only one RCT with ilaprazole assessed heartburn relief, it could not be analyzed.

3.5.2. Overall Symptom Improvement. Trials reporting cure of all APD symptoms were assessed in patients with NERD and had similar results when the outcome was focused on

Table 1: Study population characteristics of 31 included trials (41 treatment arms) for the treatment of acid peptic disease (APD).

Study arm	Reference	Type APD	Nos.	Setting	Age (yrs)	Country	1° outcome	Ome dose	Duration (wks)[a]	Control	Control dose	Attrition (%)
1a	Armstrong 2004–20 mgE	NERD	2645	Out	18–83	10 mixed	No heartburn	20	4	ESO20	20	Nr
1b	Armstrong 2004–40 mgE	—			—		—	20	4	ESO40	40	—
2	Bardhan 2001	EO	327	Out	≥18	UK, Ir, SA	Symp relief	20	4[a]	PAN20	20	19
3	Bate 1996	NERD	209	Nr	18–80	UK, Ir	No heartburn	20	4	Placebo	0	20
4a	Carlsson 1998–10 mgO	NERD	261	Nr	18–80	Au, H, N, UK	Symp relief	10	4	Placebo	0	6
4b	Carlsson 1998–20 mgO	—			—		—	20	4	Placebo	0	—
5a	Catalano 1999–40 mgP	DU	243	Nr	18–75	Italy	Ulcer healed	40	1.5	PAN40	40	8
5b	Catalano 1999–80 mgP	—			—		—	40	1.5	PAN80	80	—
6	Catalano 2000	DU	172	Nr	19-20	Italy	Ulcer healed	40	4	PAN80	80	21
7	Chang 1995	DU	111	Out	21–75	Taiwan	Ulcer healed	20	4	LAN30	30	4
8	Chen C 2017	DU	80	Nr	20–60	China	Ulcer healed	20	4	ILA10	10	Nr
9	Chen S 2017	DU	60	Nr	18–71	China	Ulcer healed	20	8	PAN40	40	Nr
10	Dekkers C 1999	EO	202	Nr	≥18	10 Euro	Erosion healed	20	4[a]	RAB20	20	5
11	Ekstrom 1995	DU	279	Nr	18–80	Sweden	Ulcer healed	20	4	LAN30	30	16
12a	Ho K 2009-5 mgI	DU/GU	518	Nr	18–80	5 Asian	Ulcer healed	20	4	ILA5	5	32
12b	Ho 2009–10 mgI	—			—		—	20	4	ILA10	10	—
13	Huang 2010	DU	120	Mixed	20–65	Mongolia	Ulcer healed	20	4	PAN40	40	Nr
14a	Kahrilas 2000–20 mgE	EO	1960	Nr	Adults	USA	Erosion healed	20	4[a]	ESO20	20	8
14b	Kahrilas 2000–40 mgE	—			—		—	20	4	ESO40	40	—
15	Li 2010	DU/PU	100	Nr	16–70	China	Ulcer healed	20	4	PAN40	40	0
16	Liao 2015	DU	80	Out	22–76	China	Ulcer healed	20	4	ILA10	10	Nr
17a	Lind 1997–10 mgO	NERD	509	Nr	≥18	Sw, Den	No heartburn	10	4	Placebo	0	5
17b	Lind 1997–20 mgO	—			—		—	20	4	Placebo	0	—
18	Mossner 1995	EO	286	Nr	≥18	Germany	Erosion healed	20	4[a]	PAN40	40	1
19	Pei 1995	DU	72	Nr	21–70	China	Ulcer healed	20	4	LAN30	30	Nr
20	Petite 1993	DU	144	Mixed	≥18	France	Ulcer healed	20	2[a]	LAN30	30	6
21	Rehner 1995	DU	286	Nr	≥18	Germany	Ulcer healed	20	2[a]	PAN40	40	3
22a	Richter 2000–10 mgO	NERD	359	Nr	≥18	USA	No heartburn	10	4	Placebo	0	1
22b	Richter 2000–20 mgO	—			—			20	4	Placebo	0	—
23a	Uemura 2008–10 mgO	NERD	284	Nr	≥20	Japan	No heartburn	10	4	Placebo	0	5
23b	Uemura 2008–20 mgO	—			—			20	4	Placebo	0	—
24	Wang L 2012	DU	494	Nr	18–65	China	Ulcer healed	20	4	ILA10	10	5
25	Watson 1997	NERD	19	Out	22–79	Ir	Symp better	40	4	Placebo	0	16
26	Xiao 1997	GU/DU	188	Nr	16–68	China	Ulcer healed	20	4–6[b]	LAN30	30	Nr
27	Xu 2006	DU	68	Out	15–78	China	Ulcer healed	20	4	RAB20	20	Nr
28	You QX 2006	DU	72	Out	18–75	China	Ulcer healed	20	4	RAB20	20	Nr
29	Zhao 2013	DU	76	Nr	29–69	China	Ulcer healed	20	4	PAN40	40	Nr
30a	Zheng 2009–30 mgL	EO	275	Nr	36–85	China	Erosion healed	20	8	LAN30	30	4
30b	Zheng 2009–40 mgP	—			—			20	8	PAN40	40	—
30c	Zheng 2009–40 mgE	—			—			20	8	ESO40	40	—
31	Zou 2012	DU	40	Nr	19–62	China	Ulcer healed	20	4	PAN40	40	Nr

Notes. [a]Duration, patients unresponsive to initial duration of treatment had extended 2–4 weeks of treatment (outcome was determined at original time of treatment not extended time); [b]4 weeks if DU and 6 weeks if GU. dy, days; DU, duodenal ulcer; EO, erosive oesophagitis; ESO, esomeprazole; GU, gastric ulcer; ILA, ilaprazole; LAN, lansoprazole; NERD, nonerosive reflux disease; Nr, not reported in paper; mixed, inpatients and outpatients; OME, omeprazole; out, outpatients; PAN, pantoprazole; PU, peptic ulcer; RAB, rabeprazole; symp, symptoms; wks, weeks; yrs, years. Countries: Asian, varied Asian countries; Au, Australia; Den, Denmark; Euro, varied European countries; H, Holland; Ir, Ireland; SA, South Africa; Sw, Sweden; UK, United Kingdom, US, United States of America; mixed, mixed geographic areas.



NOTE: Weights and between–subgroup heterogeneity test are from random–effects model; continuity correction applied to studies with zero cells

Figure 2: Forest plot of heartburn resolution by omeprazole vs. controls. Eso, esomeprazole; Lan, lansoprazole; Pan, pantoprazole; Rab, rabeprazole.

heartburn relief. Only six trials reported this outcome (Supporting Information Table 4). Our meta-analysis found that omeprazole had significantly higher rates of overall symptom improvement (RR = 1.87, $p = 0.049$, and $I^2 = 66\%$) compared to placebo (Supporting Information Figure 2). Omeprazole was equally effective compared to esomeprazole (RR = 0.96 and $p = 0.11$). Due to the paucity of trials for pantoprazole and ilaprazole with this outcome, a comparison to omeprazole was not possible. Only two trials measured improvement in symptoms scores, but no raw data were provided [39, 65].

3.5.3. Ulcer/Erosion Healing. Efficacy for the healing of ulcers was assessed in 19 trials (21 arms) and healing of lesions in patients with EO was assessed in 5 trials (8 arms) (Supporting Information Table 5). No significant publication bias was

found in trials assessing ulcer/erosion healing, Egger's test = −0.42, and $p = 0.68$ (Supporting Information Figure 3). The challenge in assessing ulcer and erosion healing was that trials used different definitions of healing (Supporting Information Table 6). For our meta-analysis, we standardized the definition of "ulcer healing" as healing of the ulcer with or without inflammation and/or scarring stage seen by endoscopy and "erosion healing" as complete epithelialization or no mucosal breaks seen in patients with EO after treatment. Using a fixed-effects model, omeprazole had equivalent healing rates (Figure 3) compared to pantoprazole (RR = 1.04 and $p = 0.12$), ilaprazole (RR = 0.96 and $p = 0.26$) and rabeprazole (RR = 1.00 and $P = 0.99$). Omeprazole showed a trend for better ulcer/erosion healing compared to lansoprazole (RR = 0.94, 95% CI: 0.89 and 0.98, $I^2 = 0\%$, and $p = 0.09$). Esomeprazole had significantly better healing rates of lesions compared to omeprazole in the three treatment arms of patients with EO (RR = 0.89, 95% CI: 0.84 and 0.93, $I^2 = 13.6\%$, and $p < 0.001$). Subgroup analysis indicated significant differences were found depending upon the type of PPI control ($X^2 = 16.2$ and $p = 0.002$). When trials assessing ulcer healing in patients with PU/DU were analyzed separately from EO, no significant differences from those above were found. No trials using placebo controls were found for patients with ulcers or EO.

3.6. Efficacy of Secondary Outcomes. Sufficient data were available to analyze the safety and cost effectiveness of omeprazole. Other secondary outcomes were not reported consistently in trials and when subgrouped by the type of PPI controls and had insufficient trials to be assessed (Supporting Information Table 7). Only two trials reported patient satisfaction [36, 52], four reported night/day time acid break-through [36, 38, 45, 49], and five trials reported the use of rescue medications [38, 39, 42, 46, 55].

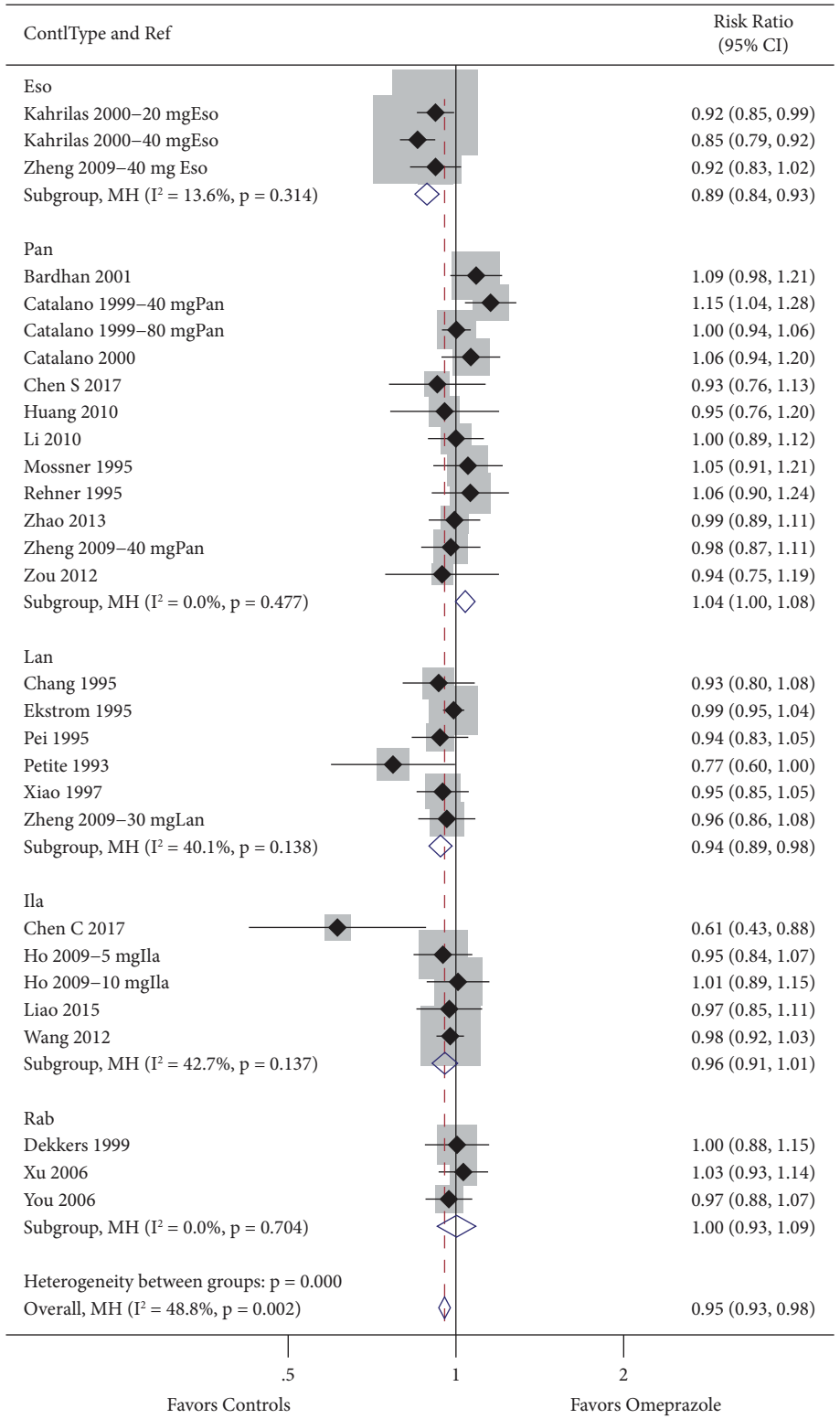
3.6.1. Safety. Adverse events or safety data were not reported in 4 (13%) trials; only a statement that "no adverse events were found" was reported in two trials (6%), no overall adverse event rate was reported in 3 trials (10%), and the types of adverse events by the treatment group was reported in 22 (71%) of trials (Supporting Information Table 8). The incidence of at least one reported adverse event was significantly lower in patients treated with omeprazole (11/100) compared to other PPIs (range: 17–31/100), Table 2. Ilaprazole reported a low but significantly higher incidence of serious adverse events (1.5%) when compared to omeprazole (0.4%). Omeprazole also reported significantly less reported nausea compared to pantoprazole (3.6% versus 8.4%, respectively). Our meta-analysis using a fixed-effects model found that the risk of adverse events was equivalent when omeprazole was compared to placebo and the other five types of PPI ($X^2 = 2.09$ and $p = 0.84$, as seen in Supporting Information Figure 4). There was no publication bias found for trials reporting adverse event data (Supporting Information Figure 5) (Egger's test = 0.87 and $p = 0.4$).

3.6.2. Direct Costs of Treatments. Direct costs of PPIs/patient based on standard recommended doses and a 4-week duration of treatment found that omeprazole (20 mg/d) was the most cost-effective PPI (89.6 Indian rupees), followed by esomeprazole (305.2 rupees), then pantoprazole (322 rupees), followed by ilaprazole (450.8 rupees), rabeprazole (498.4 rupees), and lansoprazole (876.4 rupees) (Supporting Information Table 9). Even when failure rates and retreatment costs were included, omeprazole remained the most cost-effective PPI in India.

3.7. Subgroup Analyses. Sufficient data were available to analyze efficacy of omeprazole for geographic region, degree of blinding, and study quality. There was a trend ($X^2 = 9.36$, $p = 0.096$) that omeprazole was more effective when trials were conducted in European countries compared with Asian countries, especially when compared against pantoprazole (RR = 1.07, 95% CI: 1.00–1.13, and $p = 0.035$ and RR = 0.97, 95% CI: 0.89, 1.06, and $p = 0.52$, respectively), as shown in Supporting Information Figure 6. Most trials used 20 mg/d and the limited number of trials assessing different doses of PPIs did not allow analysis of other doses. The degree of blinding (double blinded versus open) did not significantly change efficacy outcomes by the type of PPI control, but the placebo control (which was double-blinded) was significantly different ($X^2 = 91.1$, $p < 0.001$), as shown in Supporting Information Figure 7.

3.7.1. Study Quality. Of the 31 RCTs (21, 68%) were ranked overall as low risk of bias (Supporting Information Table 10) and 10 (32%) had an overall high risk of bias. Domains of high-risk included the randomization process not well described (10 trials) and due to nonblinded study designs (12 open trials). When high risk trials were excluded, omeprazole still showed significantly better heartburn resolution compared to placebo (RR = 2.47 and $p < 0.001$, Supporting Information Figure 8) and for ulcer/erosion, healing compared to pantoprazole (RR = 1.05 and $p = 0.03$, Supporting Information Figure 9). Esomeprazole was significantly better than omeprazole for ulcer/erosion healing in low-risk trials (RR = 0.88 and $p = 0.001$).

3.8. Therapeutic Effects of Omeprazole. A total of 4606 patients were treated with omeprazole in the 31 included trials. Comparing the use of omeprazole in patients with NERD to those with erosive disease (Table 3); more patients responded to 20 mg/d of omeprazole if they had erosive disease (77% healed) compared to 59% with NERD. Resolution of symptoms was significantly higher for patients with erosive disease at both two and four weeks (74% and 92.3%, respectively) compared to patients with NERD (44% and 65%, respectively). More patients with erosive disease reported no nocturnal acid breakthroughs compared to NERD (57% and 32%, respectively). *H. pylori* was successfully eradicated in 87% of the trials when omeprazole was included in the treatment strategy of patients with erosive disease [40, 41, 47, 59]. Only two trials surveyed patients for



NOTE: Weights and between–subgroup heterogeneity test are from Mantel–Haenszel model

Figure 3: Healing of ulcers and erosions by omeprazole compared to controls: forest plot. Eso, esomeprazole; Ila, ilaprazole; Lan, lansoprazole; Pan, pantoprazole; Rab, rabeprazole.

Table 2: Incidence rate (per 100) of adverse events by the type of PPI and the placebo group.

Adverse events	Omeprazole	Esomeprazole	Ilaprazole	Lansoprazole	Pantoprazole	Rabeprazole	Placebo
At least one AE reported[a]	11.0	0*	17.0*	6.7	20.1*	17.1*	30.9*
Number of SAE reported[b]	0.4	0	1.5	0	0.2	0.7	0.6
Most common types of AE reported[c]							
Headache	6.6	0	2.5	4.7	2.6*	2.2*	11.5*
Diarrhea	6.0	4.9	1.9*	0.7*	5.9	2.2	4.9
Loss of appetite	4.3	0	1.2	0	0	0	0
Nausea	3.6	0	0	2.6	8.4*	0	6.5
Constipation	1.6	0	0	4.5	0	0	4.4
Dizziness	1.6	0	0	4.1	0	0	2.7
Rash	1.1	0	0	1.8	5.0	3.0	0

*Significantly different compared to omeprazole ($p < 0.05$), AE, adverse events. [a]Data from 23 trials with overall AE rate data reported. [b]Data from 15 trials with reported SAE data. [c]Data from 19 trials with type of AE data.

Table 3: Therapeutic effects of omeprazole in 4606 patients with nonerosive or erosive acid peptic disorders.

Factors	Nonerosive reflux disease (NERD) ($n = 2286$) (%)	Erosive disease (EO/ulcers) ($n = 2320$) (%)	p value
Frequency of use			
Number taking omeprazole (20 mg/d)	64	92	
Duration omeprazole (4 weeks)	100	77	
Response to omeprazole treatment			
Healed with 20 mg/d omeprazole	59	77	<0.001
Median days to pain resolution[a]	2-3 days	3-4 days	ns
Response time[b]			
At 1 week	nr	58.8	
At 2 weeks	43.9	74	<0.0001
At 4 weeks	65.3	92.3	
At 6 weeks	60	Nr	<0.0001
At 8 weeks	94.1	Nr	
Resolution of pain by 4 weeks	90	89.7	ns
No nocturnal acid breakthrough	32	57	<0.001
H. pylori eradication	nr	87.3	
Safety[c]	6.1	16.4	<0.001

d, day; mg, milligram; nr, not reported; ns, not significant. [a]Pain: NERD (dysphagia) or EO/ulcers (pain associated with ulcer or erosion). [b]Response time: NERD (time to heartburn symptom resolution) or EO/ulcers (time to pain resolution), measured at two time periods during treatment. [c]Safety: number reporting at least one adverse event (mild moderate).

their satisfaction with omeprazole treatment, but 78% reported positive satisfaction [36, 52]. Use of rescue medications was less frequent in patients treated with omeprazole compared to other PPIs or standard treatments [38, 39, 55]. Use of omeprazole was also well tolerated (Table 3) but more patients with erosive disease reported mild-moderate adverse events (16%, $p < 0.001$) compared to patients with NERD (6%).

4. Discussion

Our systematic review and meta-analysis found that omeprazole has maintained its role as an effective treatment for the healing of heartburn and ulcers/erosions in patients with APD. In India, omeprazole is the only oral PPI listed in the National List of Essential Medicines [67]. Omeprazole was significantly more effective for heartburn relief when compared to placebo and was equivalent to the other four types of PPIs. Omeprazole also was significantly more effective to placebo for the overall improvement in APD symptoms and was equivalent to the other types of PPIs. For the resolution of ulcers or erosions, omeprazole was comparable to most of the other types of PPIs but had a trend for better healing when compared to lansoprazole. Esomeprazole was significantly better than omeprazole for ulcer healing and heartburn relief. Edwards et al. reported higher efficacy of esomeprazole (40 mg) over omeprazole (20 mg) in 12 trials with patients with severe RO (OR = 1.84, 95% CI: 1.5 and 2.2) [68]. A dose of the single S-enantiomer (esomeprazole) results in a greater body exposure when compared to an equal mg dose of the racemate, omeprazole. Hence, it is not surprising in all studies comparing esomeprazole to omeprazole, a higher efficacy has been observed with esomeprazole.

Other meta-analyses have confirmed the effectiveness of omeprazole compared to other types of treatments for APD. Dean et al. conducted a network meta-analysis (62 RCTs) focused on duodenal ulcer healing and concluded that PPIs were superior to H2RAs or placebo [69]. Barberio et al. conducted a network meta-analysis (23 RCTs) focused on NERD and concluded that omeprazole ranked first for the relief of symptoms, with esomeprazole ranked second [70].

Omeprazole (20 mg/day) has also been found to provide quick relief and symptom control in long-term nonsteroidal anti-inflammatory drugs (NSAIDs) users [71]. Omeprazole and other PPIs can prevent bleeding associated with NSAIDs [30, 31, 71]. Zhang et al. reported a meta-analysis in patients with duodenal ulcers and concluded that ilaprazole was more effective in trials done in China, but the outcome was largely influenced by one Chinese trial with a low study quality [43] and when this trial was excluded, no significant impact by country was found [9]. This was similar to our findings, which did not find significant differences in efficacy whether the trials were done in Asia, Europe, USA, or in mixed geographic regions, except when omeprazole was more effective in trials done in Europe compared with Asia when pantoprazole was the control.

Omeprazole was found to be the most cost-effective treatment for patients with APD based on direct costs in India (89.6 rupees/patient). Omeprazole was also found to be the most cost-effective PPI in a study of Chinese patients with duodenal ulcers (USD $5.30/patient) [9].

Strengths of our meta-analysis include an extensive literature search done independently by two reviewers; detection of 12 articles not previously included in previously published PPI meta-analyses due to translation or journal access issues and use of intent-to-treat analysis data and use of only RCTs to assess efficacy. Another strength is the use of a standardized Data Extraction Form (Supporting Information Figure 10). Unlike most meta-analyses that have focused on only one type of APD [43, 69–71], another strength was the comprehensive inclusion and separate analysis by the different types of APDs in our study. Use of meta-analysis subgroups allowed omeprazole to be compared to each type of PPI or placebo separately.

Limitations of our meta-analysis are related to the exclusion of trials that did not share common outcomes. While most trials reported common outcomes (heartburn symptom relief and/or ulcer/erosion healing), some trials had uncommon outcome measures (recurrences of bleeding ulcers or pH levels or overall symptom scores). Some trials with a high risk of bias were hampered by the lack of blinding (PPI controls had different formulation from omeprazole). Another limitation was the varied definitions used for "relief of symptoms" or "ulcer healing." For example, definitions of ulcer/erosion healed included "epithelium healed," "no ulcer crater," "only residual scar," "no mucosal break," or healing categorized in four levels (ulcer healed with no inflammation, ulcer healed but inflammation present, ulcer size reduced by less than 50%, or no change in ulcer size). We attempted to minimize this by using standardized definitions across the studies based on data reported in each trial. Many outcomes for APD which may be clinically important (for example, night-time relief of symptoms or monitoring pH levels) could not be assessed as these outcomes were not commonly reported in the trials. No phase 3 RCTs could be found that were published after 2017. As no trials were done in children, these results may not be generalizable to the pediatric population.

Omeprazole use was well tolerated and had a low rate of adverse events, with only 11% of the patients reporting mild symptoms, most commonly headache or diarrhea. Omeprazole has been the most extensively studied and used, with more than 1200 clinical trials and 400 million patient treatment courses worldwide [72]. Omeprazole has an extensively documented long-term safety profile for over 30 years, is approved as treatment for most acid-related indications, and is effective for the treatment of dyspepsia as well as healing and prevention of NSAID-associated duodenal and gastric ulcers [71]. We were also not able to analyze the safety in high-risk populations (diabetic, chronic kidney disease, etc.), as none of the included trials were done in these subpopulations, but several studies did not report any increase in adverse events when used in diabetic patients with chronic kidney disease [73] or patients with cardiovascular disease [74]. Concerns with drug interactions between clopidogrel, an anticlotting medication given to cardiac patients, and proton-pump inhibitors have been raised [75]. Observational studies do not indicate an increased cardiovascular risk while combining the two drugs despite the theoretical risk of reduced availability of the active moiety of clopidogrel due to the competitive sage of CYP 2C19 by the PPI.

5. Conclusions

Omeprazole is an effective and safe treatment for acid peptic disorders, including the rapid resolution of GERD symptoms and resolution of erosions and ulcers. Omeprazole was the most cost-effective type of PPI in India. Omeprazole's therapeutic role for patients with acid peptic disorders remains strong.

Data Availability

The data used to support the findings of this study are provided in Supporting Information Files.

Ethical Approval

This is a review paper and no ethical approval was required.

Conflicts of Interest

LM is a consultant and paid lecturer for Biocodex (France) and BioK+/Kerry (Canada), Axon Pharma SAS (South America), and Dr. Reddy's Laboratory (India) and is on the Microbiome Advisory Board (Biocodex, France) and on the Scientific Advisory Board for BioK+/Kerry, Canada. The other coauthors declare that they have no conflicts of interest.

Authors' Contributions

All authors contributed to the material preparation, data collection, data extraction, and review of the trials. Study design and data analysis were done by Lynne McFarland. The first draft of the manuscript was done by Lynne

McFarland and all authors commented on the subsequent revisions of the manuscripts. All the authors have read and approved the final manuscript.

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Supplementary Materials

Supplementary Information Table 1: PRISMA Checklist of literature search. Supplementary Information Table 2: excluded trials or treatment arms. Supplementary Information Table 3: frequency of heartburn healing in included trials. Supplementary Information Table 4: improvement in all symptoms as an outcome in patients with nonerosive NERD. Supplementary Information Table 5: outcomes for ulcer healing in patients with erosive ulcers and erosion healing for patients with erosive oesophagitis. Supplementary Information Table 6: definitions of ulcer healing in included trials. Supplementary Information Table 7: other reported outcomes in included trials. Supplementary Information Table 8: frequency of adverse event reporting in included trials. Supplementary Information Table 9: direct costs of PPI treatments based on included trials for patients with acid peptic disorders. Supplementary Information Table 10: risk of bias in included trials. Supplementary Information Figure 1: funnel plot of publication bias for trials with outcome: improvement in heartburn symptoms. Egger's test ($p < 0.001$) indicates possible bias. Supplementary Information Figure 2: improved symptoms in NERD patients comparing omeprazole to other controls. Supplementary Information Figure 3: funnel plot for publication bias of trials with outcome: erosion or ulcer healing. Supplementary Information Figure 4: forest plot of relative risk of no adverse events of omeprazole compared to controls. Supplementary Information Figure 5: funnel plot of publication bias for trials reporting any adverse reaction data. Supplementary Information Figure 6: ulcer healing by country where trial was conducted and by the type of proton-pump inhibitor. Supplementary Information Figure 7: subgroup degree of blinding for heartburn relief. Supplementary Information Figure 8: trials with low risk of bias for outcome: heartburn symptoms relieved/improved/cured. Supplementary Information Figure 9: trials with low risk of bias for outcome erosion/ulcer healed. Supplementary Information Figure 10: Data Extraction Form. (*Supplementary Materials*)

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