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Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies

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SUMMARY

Background
Over-the-counter histamine-2 receptor antagonists, antacids and alginate/antacids are commonly used for gastro-oesophageal reflux disease.

Aim
To conduct a systematic review and meta-analysis of related treatment trials.

Methods
We performed a systematic search and abstraction of randomized, placebo-controlled trials conducted during 1972–2005. Study quality was measured by the Jadad score (0–5). Results were pooled using random effects model.

Results
Ten trials ($n = 3442$, placebo = 2940; Jadad score 3.5) showed a higher response with histamine-2 receptor antagonists in regard to complete relief of heartburn, symptomatic improvement, and episodes requiring rescue antacids. The absolute benefit increase was 10–12% and relative benefit increase was 19–41%. Four trials ($n = 578$, placebo = 577; Jadad score 3.5) showed a trend in favour of antacids in symptomatic improvement (absolute benefit increase 8%, 95% CI: 0–16%; relative benefit increase 0.11) and requirement of rescue antacids (OR 0.70, 95% CI: 0.59–0.84). Four trials ($n = 146$, placebo = 138; Jadad score 3.8) found alginate/antacid combination superior to placebo in symptomatic improvement (absolute benefit increase 26%, 95% CI: 12%–41%, relative benefit increase 0.60).

Conclusions
Over-the-counter medications are effective in treating symptomatic gastro-oesophageal reflux disease. Compared with the placebo response, which ranged between 37% and 64%, the relative benefit increase was up to 41% with histamine-2 receptor antagonists, 60% with alginate/antacid combinations, and 11% with antacids.

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a common medical condition, affecting an estimated 44% of individuals in the US at least once a month according to a Gallup survey.[1] Up to 18 million adults in the US are estimated to take some type of indigestion remedy at least twice a week.[1] The options for over-the-counter (OTC) medications are numerous and include antacids in myriad formulations, alginate with or without antacids, histamine-2 receptor antagonists (H2RAs), and more recently proton pump inhibitors (PPIs). Some of these products such as recently marketed, omeprazole have been extensively tested, and have well-known efficacy data. However, other therapies have been in existence for over 50 years, and their efficacy is less clear. Although, many studies have evaluated the efficacy of individual OTC GERD therapies, there have been no systematic reviews of these studies. In this systematic review and meta-analysis, we evaluated randomized trials that examined the efficacy of several OTC GERD therapies, namely antacids, alginates and H2-blockers.

MATERIALS AND METHODS

Two investigators independently searched the medical literature from 1972 to 2005 by using the MEDLINE database. We limited the search to randomized-controlled trials conducted in adults (19 years of age and above) and published in English. Search terms included GERD OR GORD OR gastro-oesophageal reflux disease OR gastro-oesophageal reflux disease OR reflux AND antacid OR alginate OR histamine-2 receptor antagonist AND placebo NOT PPI. The initial citations from the MEDLINE searches were reviewed independently by two investigators for potentially relevant articles. Detailed standardized data abstraction was also performed independently by two investigators. The following inclusion criteria were applied: (i) randomized-controlled trials comparing antacid, alginate/antacid combination, or H2RA at OTC doses to a placebo; (ii) outcomes of interest including complete and adequate relief of GERD symptoms, subjective global improvement, and the use of rescue antacids. The following exclusion criteria were applied: (i) the use of prescription-strength or high-dose GERD agents; (ii) the lack of well-defined outcomes of interest; and (iii) duplicated articles. We performed a hand search of cited bibliographies, including abstracts presented at major meetings. We also supplemented the search by contacting US manufacturers for unpublished data. Study qualities were measured by the Jadad scoring system (from 0 to 5).[2]

Data on treatment and outcomes were extracted, tabulated, and meta-analysed by using a random-effects model. The data search, abstraction and analyses were conducted according to a standardized protocol. Differences were resolved by consensus. For each meta-analysis, the combined absolute benefit increase (ABI), relative benefit increase (RBI) and number needed to treat (NNT) of treatment compared with placebo were calculated. The ABI was calculated as the difference between experimental and control event rates. The RBI was calculated as (experimental event rate – control event rate)/control event rate. The NNT was defined as the number of subjects to treat in order to gain one good outcome and was calculated as the inverse of the ABI. For meta-analyses of the outcome 'use of rescue antacids', odds ratios were calculated. We evaluated heterogeneity among studies in each meta-analysis using a chi-squared test; P-values of <0.1 were considered to be significant for heterogeneity. Heterogeneity was further evaluated by calculating the I^2 statistic; $I^2 = [(Q-\text{d.f.})/Q] \times 100\%$, where Q is the chi-squared statistic and d.f. is degrees of freedom. I^2 identifies the percentage of variability in effect because of heterogeneity rather than sampling error. I^2-values >50% are generally considered substantial heterogeneity. Funnel plots were used to assess the publication bias. We performed the statistical analyses with Comprehensive Meta-Analysis (Biostat, Engelwood, NJ, USA).

RESULTS

The MEDLINE search initially yielded 693 citations. After the preliminary review by two independent reviewers, 47 articles were deemed to be potentially relevant and were reviewed in detail. A total of 38 articles were excluded (29 for the use of high-dose H2RA agents, eight for the lack of outcomes of interest, and one for duplication), leaving nine studies to be included in our review.[3–11] A hand search of cited bibliographies resulted in four additional articles that met inclusion and exclusion criteria.[12–15] A contact of US manufacturers of antacids, alginates, and H2-blockers resulted in one unpublished study that met inclusion and exclusion criteria.[16] Overall, we reviewed 14 papers containing 18 comparisons. Four of these papers had multiple arms evaluating different

Table 1. Summary of the 10 trials that compared 4 histamine-2 receptor antagonist agents to placebo. All data were based on intention-to-treat analysis

Author/design	Main drug (*n*)	Comparator (*n*)	Outcome measurement	Endpoints	Results main drug	Results comparator	*P*-values	Jadad score
Spiegel[9] (1997) US R, DB, PC, PG	Nizatidine 75 mg (Axid AR), single dose 30 min before a provocative meal $n = 101$	Placebo $n = 103$	(i) Presence of heartburn (ii) Heartburn severity on visual analog scale (0–100 mm)	(i) Subjects with complete prevention of heartburn (ii) Longest duration of no heartburn (iii) Total duration of no heartburn (iv) Mean heartburn severity (v) Peak heartburn severity	(i) 15/101 (15%) (ii) 85 min (iii) 85 min (iv) 18 mm (v) 30 mm	(i) 3/103 (3%) (ii) 30 min (iii) 40 min (iv) 40 mm (v) 80 mm	(i) <0.001 (ii) <0.001 (iii) <0.001 (iv) <0.001 (v) <0.001	3
Pappa[6, 7](1999) US R, DB, PC, PG	Ranitidine 75 mg (Zantac 75), single dose 30 min before a provocative meal $n = 145$	Placebo $n = 139$	(i) Presence of heartburn (ii) Heartburn severity visual analog scale (0–100 mm) (iii) Six-point scale of global assessment	(i) Subjects with area under the concentration curve <50 mm/h (ii) Peak heartburn severity (iii) % reduction in peak heartburn severity (iv) Subjects with treatment assessments of good or better (v) Subjects with complete prevention of heartburn	(i) 96/145 (66%) (ii) 28.7 mm (iii) 52% (iv) 106/145 (73%) (v) 23/145 (16%)	(i) 63/139 (45.3%) (ii) 42.4 mm (iii) 29.8% (iv) 79/139 (57%) (v) 7/139 (5%)	(i) <0.001 (ii) <0.001 (iii) <0.001 (iv) <0.001 (v) 0.006	2
Pappa[15] (1998) US R, DB, PC, PG	Ranitidine 75 mg (Zantac 75), single dose 60 min before a meal $n = 148$	Placebo $n = 148$	(i) Presence of heartburn (ii) Heartburn severity visual analog scale (0–100 mm) (iii) Six-point scale of treatment efficacy	(i) Heartburn severity measured by area under the concentration curve (ii) Mean % reduction in heartburn severity (iii) Peak heartburn severity (iv) % reduction in peak heartburn severity (v) Efficacy ratings of good or better	(i) 43.7 mm.h (ii) 60.8% (iii) 26.6 mm (iv) 53.3% (v) 105/148 (71%)	(i) 73.9 mm.h (ii) 41.2% (iii) 37.6 mm (iv) 38.7% (v) 83/148 (56%)	(i) <0.001 (ii) <0.001 (iii) <0.001 (iv) <0.002 (v) <0.004	3
Galmiche[8] (1998) France R, DB, PC, PG	Ranitidine 75 mg (Zantac 75), up to three times a day as needed over 15 days $n = 504$	Placebo $n = 270$	(i) Heartburn severity visual analog scale (0 mm, none, to 100 mm, severe) (ii) Home diary for # of daily episodes, # of doses taken, time to relief onset and duration of relief	(i) Subjects with relief of at least 75% of heartburn episodes within 2 h. of drug ingestion for at least 5 h (ii) Subjects with any heartburn relief (iii) Subjects with symptomatic improvement (iv) Total # of heartburn episodes (v) Subjects who rated treatment effective or very effective (vi) Subjects who used rescue antacids	(i) 207/504 (41%) (ii) 423/504 (84%) (iii) 443/504 (88%) (iv) 17.0 (v) 393/504 (78%) (vi) 186/504 (37%)	(i) 76/270 (28%) (ii) 207/270 (77%) (iii) 237/270 (88%) (iv) 18.7 (v) 170/270 (63%) (vi) 138/270 (51%)	(i) <0.001 (ii) <0.05 (iii) N.S. (iv) N.S. (v) <0.001 (vi) <0.001	4

Table 1. (Continued)

Author/design	Main drug (n)	Comparator (n)	Outcome measurement	Endpoints	Results main drug	Results comparator	P-values	Jadad score
Galmiche[8] (1998) France R, DB, PC, PG	Cimetidine 200 mg (Tagamet), up to three times a day as needed over 15 days $n = 515$	Placebo $n = 270$	(i) Heartburn severity visual analog scale (0 mm, none, to 100 mm, severe) (ii) Home diary for # of daily episodes, # of doses taken, time to relief onset and duration of relief	(i) Subjects with relief of at least 75% of heartburn episodes within 2 h. of drug ingestion for at least 5 h (ii) Subjects with any heartburn relief (iii) Subjects with symptomatic improvement (iv) Total # of heartburn episodes (v) Subjects who rated treatment effective or very effective (vi) Subjects who used rescue antacids	(i) 201/515 (39%) (ii) 417/515 (81%) (iii) 453/515 (88%) (iv) 16.8 (v) 402/515 (78%) (vi) 206/515 (40%)	(i) 76/270 (28%) (ii) 207/270 (77%) (iii) 237/270 (88%) (iv) 18.7 (v) 170/270 (63%) (vi) 138/270 (51%)	(i) <0.01 (ii) N.S. (iii) N.S. (iv) N.S. (v) <0.001 (vi) <0.001	4
Paul[4] (2001) US R, DB, PC, PG	Nizatidine 75 mg (Axid AR), up to two times a day as needed over 2 weeks $n = 498$	Placebo $n = 496$	(i) Home diary to record heartburn relief	(i) Sustained adequate relief score for 1st four heartburn episodes for at least 3 h using a 5- point scale (ii) % of each heartburn episode with adequate relief (iii) % of heartburn episodes with complete relief at 3 h (iv) % of each heartburn episode where antacids were used (v) Subjects with complete relief of all heartburn episodes	(i) 2.43 (ii) 75% (iii) 74% (iv) 20% (number of heartburn episodes not provided) (v) 184/498 (37%)	(i) 2.14 (ii) 66% (iii) 64% (iv) 27% (number of heartburn episodes not provided) (v) 119/496 (24%)	(i) <0.001 (ii) <0.001 (iii) <0.001 (iv) <0.001 (v) <0.001	4
Pappa[6, 7] (1999) US R, DB, PC, PG	Ranitidine 75 mg (Zantac 75), up to four times a day as needed over 2 weeks $n = 491$	Placebo $n = 494$	(i) Home diaries to record heartburn severity and duration	(i) Subjects with no bothersome heartburn symptoms within 1 h of drug ingestion that lasted for at least 3 h (ii) Onset of relief (iii) Subjects who used rescue antacid	(i) 280/491 (57%) (ii) 30′-147/491 (30%), 45′-206/491 (42%), 60′-280/491 (57%) (iii) 98/491 (20%)	(i) 207/494 (42%) (ii) 30′-108/494 (22%), 45′-153/494 (33%), 60′-207/494 (42%) (iii) 163/494 (33%)	(i) <0.001 (ii) <0.001 for all episodes (iii) <0.05	3

Table 1. (Continued)

Author/design	Main drug (*n*)	Comparator (*n*)	Outcome measurement	Endpoints	Results main drug	Results comparator	*P*-values	Jadad score
Korn[16] (2000) US R, DB, PC, PG	Famotidine 10 mg (Pepcid AC), up to two times a day over 2 weeks $n = 406$ subjects $n = 1598$ heartburn episodes	Placebo $n = 399$ subjects $n = 1533$ heartburn episodes	(i) Home diary card to record heartburn relief (ii) 5-point effectiveness scale	(i) Time to adequate relief (ii) Heartburn episodes with adequate relief for at least 7 h (iii) % of heartburn episodes treated with rescue antacid (iv) Subjects with treatment rating of good or excellent	(i) 15′-430/1598 (27%), 30′-734/1598 (46%), 45′-1013/1598 (67%), 60′-1201/1598 (74%) (ii) 960/1598 (60%) (iii) 542/1598 (33.9%) (iv) 292/406 (72%)	(i) 15′-386/1533 (25%), 30′-651/1533 (43%), 45′-1042/1533 (62%), 60′-1229/1533 (74%) (ii) 790/1533 (51%) (iii) 658/1533 (42.9%) (iv) 259/398 (65%)	(i) OR 1.12 (95% CI 0.92–1.36, N.S.) (ii) OR 1.37 (95% CI: 1.14–1.65, $P < 0.05$) (iii) N.A. (iv) N.A.	5
Ciociola[3] (2001) US R, DB, PC, PG	Ranitidine 75 mg (Zantac 75), up to four times a day over 2 weeks $n = 516$	Placebo $n = 510$	(i) Home diaries to record time of heartburn onset, heartburn severity (mild, moderate, severe) and onset of relief	(i) Subjects with adequate relief of heartburn within 1 h of drug ingestion that lasted for at least 3 h (ii) Onset of treatment success (iii) % of heartburn episodes for which subject took rescue antacids (iv) Subjects with successfully treated nocturnal symptoms	(i) 272/516 (53%) (ii) 15′-61/516 (11.8%), 30′-136/516 (26%), 45′-206/516 (40%) (iii) 109/513 (21%) (iv) 320/516 (77%)	(i) 214/510 (42%) (ii) 15′-52/510 (10%), 30′-114/510 (22.4%), 45′-170/510 (33%) (iii) 164/510 (32%) (iv) 351/510 (69%)	(i) <0.001 (ii) 15′-$P = 0.346$ 30′-$P = 0.028$ 45′-$P < 0.001$ (iii) <0.001 (iv) 0.014	3
Simon[14] (1995) US R, DB, PC, PG	Famotidine 10 mg (Pepcid AC), up to two times a day over 4 weeks $n = 113$ subjects $n = 553$ heartburn episodes	Placebo $n = 111$ subjects $n = 553$ heartburn episodes	(i) Home diaries to record heartburn relief hourly and the use of backup antacid	(i) Heartburn episodes relieved (ii) Odd ratio for more rapid and more frequent relief (iii) Subjects with treatment rating of good or excellent (iv) Heartburn episodes for which subjects took rescue antacids	(i) 387/553 (70%) (ii) 1.94 (iii) 84/113 (74%) (iv) 144/553 (26%)	(i) 227/553 (41%) (ii) 1 (iii) 70/111 (63%) (iv) 228/553 (43%)	(i) <0.001 (ii) <0.001 (iii) N.S. (iv) <0.001	4

US, United States; R, randomized; DB, double-blinded; PC, placebo-controlled; PG, parallel-group.

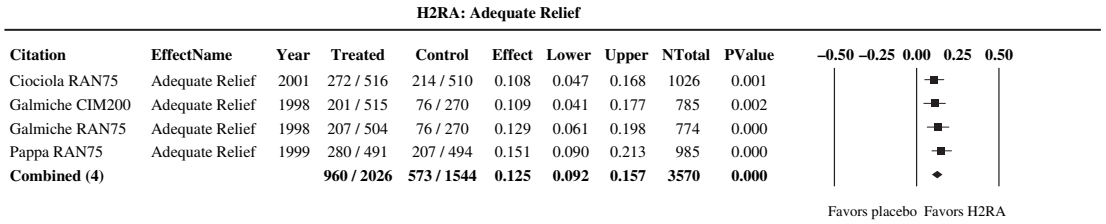

Figure 1. Forest plot showing findings of randomized-controlled trials that compared adequate relief of heartburn by histamine-2 receptor antagonists vs. placebo taken over 2 weeks to 4 weeks. Tests of heterogeneity: $Q = 1.24$, d.f. $(Q) = 3$, $P = 0.74$, $I^2 = 0\%$. RAN75: ranitidine 75 mg, CIM200: cimetidine 200 mg.

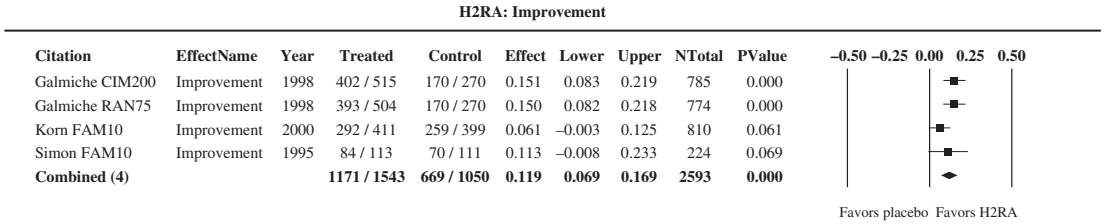

Figure 2. Forest plot showing findings of randomized-controlled trials that compared the improvement of heartburn by histamine-2 receptor antagonists vs. placebo taken over 2 weeks to 4 weeks. Tests of heterogeneity: $Q = 4.77$, d.f. $(Q) = 3$, $P = 0.19$, $I^2 = 37\%$. CIM200: cimetidine 200 mg, RAN75: ranitidine 75 mg, FAM10: famotidine 10 mg.

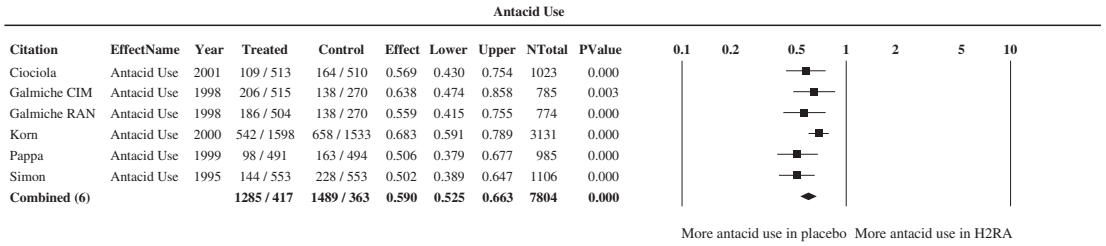

Figure 3. Forest plot showing findings of randomized placebo-controlled trials of histamine-2 receptor antagonists that examined the use of rescue antacids. Tests of heterogeneity: $Q = 6.74$, d.f. $(Q) = 5$, $P = 0.24$, $I^2 = 26\%$.

treatment agents.[8, 13, 14, 16] For example, one arm of the trial by Simon *et al.*[14] evaluated an OTC H2RA while another arm evaluated an antacid.

H2RAs

We identified a total of 10 randomized, placebo-controlled, double-blinded, parallel group trials ($n = 3442$, placebo = 2940) with a mean Jadad score 3.5 (range: 2–5) that compared.

Histamine-2 receptor antagonists (four different agents) vs. placebo (Table 1). These studies are categorized in two broad categories: single dose treatment and repeated doses are a 2–4-week period.

Three trials evaluated the use of H2RAs as a *single dose* given 30–60 min prior to a provocative meal.[6, 9, 15] Two of these trials examined the complete prevention of heartburn for at least 3 h after a provocative meal. The combined ABI of H2RAs over placebo was 11.3% (95% CI: 6.2–16.5%, $P < 0.0001$); the RBI was 2.7 (95% CI: 1.5–4.0); the NNT was 9 (95% CI: 6–16).[6, 9] Two trials evaluated the patients' assessment of 'improved' symptoms at the end of the treatment period. The combined ABI of H2RAs over placebo was

Table 2. Summary of the four trials that compared antacid agents to placebo

Author/ design	Main drug (*n*)	Comparator (*n*)	Symptom measurement	Endpoints	Results main drug	Results comparator	*P*-values	Jadad score
Stanciu[13] (1974) UK R, DB, PC, PG	Antacid (aluminum hydroxide/magnesium carbonate) two tablets three times a day for 2 weeks $n = 20$	Placebo $n = 20$	(i) Number of reflux episodes measured by pH probe (ii) Interview	(i) % reduction in reflux episodes (ii) Subjects with symptomatic improvement	(i) 93% (ii) 5/20 (25%)	(i) 94% (ii) 7/20 (35%)	(i) N.A. (ii) 0.49	2
Korn[16] (2000) US R, DB, PC, PG	Antacid (aluminum hydroxide/magnesium carbonate) 21 mEq up to two doses a day for 2 weeks $n = 407$ subjects $n = 1565$ heartburn episodes	Placebo $n = 399$ subjects $n = 1533$ heartburn episodes	(i) Home diary card to record heartburn relief (ii) 5-point effectiveness scale	(i) Time to adequate relief (ii) Adequate relief for at least 7 h. (iii) Heartburn episodes treated with rescue antacids (iv) Subjects with treatment rating of good or excellent	(i) 15′-508/1565 (32%), 30′-768/1565 (49%), 45′-1059/1533 (62%), 60′-1246/1565 (74%) (ii) 909/1565 (59%) (iii) 565/1565 (36.1%) (iv) 293/407 (72%)	(i) 15′-386/1533 (25%), 30′-651/1533 (43%), 45′-1042/1533 (62%), 60′-1229/1533 (74%) (ii) 790/1533 (51%) (iii) 658/1533 (42.9%) (iv) 259/398 (65%)	(i) OR 1.35 95% CI (1.10–1.65) $P < 0.05$ (ii) OR 1.35 95% CI (1.12–1.63 $P < 0.05$) (iii) 0.0001 (iv) 0.03	5
Weberg[10] (1998) Norway R, DB, PC, CO	Antacid chewable tablet (aluminum hydroxide/ magnesium carbonate) 30 mEq four times a day for 2 weeks, then placebo for two more weeks $n = 47$	Placebo $n = 47$	(i) Home diary (ii) 100-mm heartburn visual analog scale	(i) Subjects with improvement of heartburn (ii) Subjects with improvement of global symptomatic score (iii) Mean number of days with heartburn (iv) Mean number of nights with heartburn	(i) 37/46 (80%) (ii) 37/47 (79%) (iii) 6.2 (iv) 3.1	(i) 28/46 (61%) (ii) 26/47 (54%) (iii) 8 (iv) 4.2	(i) 0.07 (ii) <0.05 (iii) <0.01 (iv) <0.05	3
Simon[14] (1995) US R, DB, PC, PG	Antacid (magnesium/ aluminum hydroxide) 11 mEq to be taken up to twice daily for 4 weeks $n = 113$ subjects $n = 553$ heartburn episodes	Placebo $n = 111$ subjects $n = 553$ heartburn episodes	(i) Home diary to record heartburn relief hourly and the use of backup antacids	(i) Heartburn episodes relieved (ii) Odd ratio for more rapid and more frequent relief (iii) Subjects with treatment rating of good or excellent (iv) Heartburn episodes for which subjects took rescue antacids	(i) 343/553 (62%) (ii) 1.57 (iii) 77/113 (68%) (iv) 177/553 (32%)	(i) 227/553 (41%) (ii) 1 (iii) 70/111 (63%) (iv) 238/553 (43%)	(i) <0.05 (ii) 0.003 (iii) N.S. (iv) <0.05	4

US, United States; UK, United Kingdom; R, randomized; DB, double-blinded; PC, placebo-controlled; PG, parallel-group; CO, cross-over.

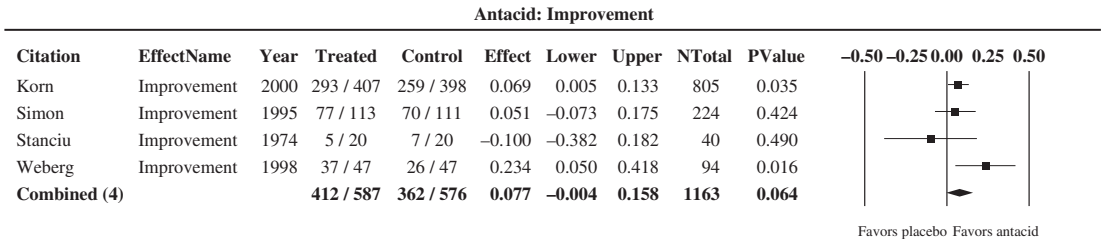

Figure 4. Forest plot showing findings of randomized-controlled trials that compared subjective improvement after 2 weeks to 4 weeks of antacid therapy vs. placebo. Tests of heterogeneity: $Q = 4.52$, d.f. $(Q) = 3$, $P = 0.21$, $I^2 = 34\%$.

16% (95% CI: 7.9–23.3%, $P < 0.0001$); the RBI was 0.29 (95% CI: 0.14–0.41); the NNT was 6 (95% CI: 4–13).[6, 15]

Seven trials evaluated the efficacy of H2RAs taken over 2 *weeks to 4 weeks*. Four trials examined the adequate relief of heartburn within 1 h of drug ingestion that lasted for at least 3 h; the combined effect favoured H2RAs (ABI 10%, 95% CI: 7%–13%, $P < 0.0001$; RBI 0.28, 95% CI: 0.19–0.36; NNT 10, 95% CI: 7–14) (Figure 1).[3, 7, 8] Only one trial evaluated the complete relief of heartburn; 37% of subjects on H2RA vs. 24% of subjects on placebo reported complete relief ($P < 0.001$).[4] Four studies evaluated subjective improvement (defined as patients' rating of the treatment of 'good/excellent' or 'effective/very effective') at the end of the treatment period; the combined effect favoured H2RAs (ABI 12%, 95% CI: 7–17%, $P < 0.0001$; RBI 0.19, 95% CI: 0.13–0.25; NNT 8, 95% CI: 6–14) (Figure 2).[8, 14, 16] The use of rescue antacids was examined in six trials.[3, 7, 8, 14, 16] Subjects on H2RAs were significantly less likely to require rescue antacids (OR 0.59, 95% CI: 0.53–0.66, $P < 0.0001$) (Figure 3). Overall, there were no significant differences between the four H2RA agents.

Antacids

Only four randomized trials (treatment = 578, placebo = 577) with a mean Jadad score 3.5 (range: 2–5) met the inclusion and exclusion criteria (Table 2). They evaluated subjective improvement (defined as rating of treatment as 'good/excellent' or global assessment of 'better/much better') after 2 weeks to 4 weeks of therapy. The combined ABI of antacid treatment over placebo was 8% (95% CI: 0–16%, $P = 0.06$). The combined RBI was 0.11 (95% CI: 0.03–0.20). The NNT was 13 (95% CI: 6–250) (Figure 4).[10, 13, 14, 16] Two trials found that subjects on antacids were less likely to have heartburn episodes requiring rescue antacids (OR 0.70, 0.59–0.84, $P < 0.0001$).[14, 16]

Alginate/antacid combination (Gaviscon)

Only four randomized trials (treatment = 146, placebo = 138) with a mean Jadad score 3.8 (range: 2–5) compared alginate/antacid combination against placebo (Table 3). Three of these trials evaluated subjective improvement after 2 weeks of treatment (defined as patients' self-assessment of 'positive response', 'better/much better', or 'improved'). The combined ABI of alginate/antacid combination over placebo was 26% (95% CI: 12–41%, $P < 0.0001$). The RBI was 0.60 (95% CI: 0.25–0.91). The NNT was 4 (95% CI: 2–9) (Figure 5).[5, 11, 13] One trial studied the role of alginate/antacid combination as therapy for postprandial heartburn; 67% of patients on alginate/antacid reported symptomatic improvement of heartburn within 15 min of drug ingestion compared with 28% of patients on placebo ($P < 0.05$).[12]

Heterogeneity tests were performed for all the calculations. In the chi-squared statistic, the *P*-values ranged from 0.2 to 0.9, suggesting that there was no significant heterogeneity in the results of these trials in any of the comparisons. The I^2-values ranged from 0% to 40%, further confirming the lack of substantial heterogeneity in these trials.

DISCUSSION

We conducted this comprehensive review to examine the efficacy of several common OTC therapies including H2RA, antacid, and alginate/antacid agents. Since 1996, all four H2RAs had been available as OTC preparations. The efficacy of H2RAs at regular or high doses in treating GERD and oesophagitis has been demonstrated.[17, 18] However, the efficacy of H2RAs at

Table 3. Summary of the four trials that compared antacid/alginate combination (Gaviscon) to placebo

Author/design	Main drug (*n*)	Comparator (*n*)	Symptom measurement	Endpoints	Results main drug	Comparator	*P*-values	Jadad score
Stanciu[1] (1974) UK R, PC, PG	Gaviscon two tablets three times a day for 2 weeks $n = 20$	Placebo $n = 20$	(i) Number of reflux episodes measured by pH probe (ii) Interview	(i) % reduction in reflux episodes (ii) Subjects with symptomatic improvement	(i) 79% (ii) 11/20 (55%)	(i) 94% (ii) 7/20 (35%)	(i) N.A. (ii) 0.2036	2
Beeley[11] (1972) UK R, DB, PC, CO	Gaviscon two tablets three times a day for 2 weeks $n = 28$	Placebo $n = 28$	(i) Interview (ii) Questionnaire	(i) Subjects with improvement of heartburn (ii) Subjects with improvement of regurgitation (iii) Preferred agent for relief of heartburn (iv) Preferred agent for relief of regurgitation	(i) 21/27 (78%) (ii) 25/28 (89% (iii) 22/26 (85%) (iv) 20/22 (91%)	(i) 14/27 (52%) (ii) 12/28 (43%) (iii) 4/26 (15%) (iv) 2/22 (9%)	(i) 0.05 (ii) 0.0002 (iii) <0.01 (iv) <0.001	4
Lanza[12] (1986) US R, DB, PC, CO	Gaviscon two tablets one time $n = 60$	Placebo $n = 60$	Nurse to record time from taking medication to complete relief of heartburn	Subjects with symptomatic improvement within 15 min	40/60 (67%)	17/60 (28%)	<0.05	4
Chatfield[5] (1999) UK R, DB, PC, PG	Gaviscon 10 mL four times a day for 2 weeks $n = 38$	Placebo $n = 30$	Diary card	Subjects with symptomatic improvement	28/38 (74%)	13/30 (44%)	0.004	5

US, United States; UK, United Kingdom; R, randomized; DB, double-blinded; PC, placebo-controlled; PG, parallel-group; CO, cross-over.

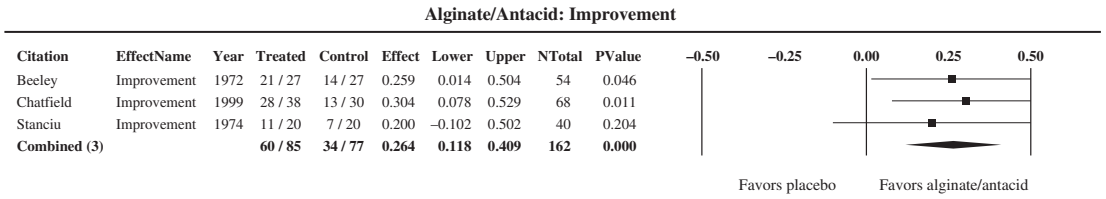

Figure 5. Forest plot showing findings of randomized-controlled trials that compared subjective improvement after 2 weeks of alginate/antacid combination vs. placebo. Tests of heterogeneity: $Q = 0.29$, d.f. (Q) = 3, $P = 0.86$, $I^2 = 0\%$.

OTC doses (half-prescription doses) has not been systematically evaluated. In our review, all the studies included for analysis are randomized, placebo-controlled, double-blinded and parallel-group to ensure the homogeneity of trial designs. When used as a single dose prior to a provocative meal, H2RAs were superior to placebo in the complete prevention of postprandial GERD symptoms with an ABI of 11% ($P < 0.0001$, NNT 9). The efficacy of H2RAs expressed as symptomatic improvement was slightly larger; the ABI was 16% ($P < 0.0001$) and the NNT was 6. When used over 2 weeks to 4 weeks, H2RAs were also superior to placebo in all clinical endpoints: adequate relief (ABI 10%, $P < 0.0001$, NNT 10), complete relief (ABI 13%, $P < 0.001$, NNT 8), subjective improvement (ABI 12%, $P < 0.0001$, NNT 8) and breakthrough GERD symptoms as suggested by a decreased use of rescue antacids (OR 0.56–0.59, $P < 0.0001$).

The efficacy of antacids is less well-established, and the quantity and quality of studies examining the efficacy of antacids are less than those for alginate and H2RA. Ironically, the best evidence for antacid efficacy comes from a recent study conducted primarily to examine the efficacy of H2RA.[16] There was a significant reduction in heartburn episodes requiring rescue antacids in groups taking antacids (OR 0.70, $P < 0.0001$). There was also a trend that fell short of statistical significance favouring antacids over placebo in patients' subjective improvement (ABI 8%, $P = 0.06$, NNT 13). A small study by Graham *et al.*[19] found no significant difference in heartburn frequency or severity. This study was not included in our meta-analysis because of the absence of a well-defined outcome. However, the small number of subjects in this study would not alter the outcome of our meta-analysis.

Alginate reacts with gastric acid to form a viscous near-neutral pH layer on the gastric contents, thus acting as a mechanical barrier between the gastric contents and the oesophagus. There are four randomized trials comparing alginate/antacid combination to placebo. The alginate/antacid combination was more efficacious than placebo both as a single premeal dose (ABI 39%, $P < 0.05$, NNT 3) and after 2 weeks of therapy (ABI 26%, $P < 0.0001$, NNT 4).

Given that the efficacy of OTC antacids and alginate was shown in prevention and treatment of postcibal symptomatic episodes, their role seems to be best suited for individuals with infrequent meal induced episodes, as well as those with breakthrough symptoms while taking other longer acting treatment. OTC H2RAs could be used with slightly increased efficacy but with a slower onset of action for the same indications. The trials for all three groups did not examine for healing of erosive oesophagitis (or its presence in the first place) and hence one cannot assume similar efficacy in the presence of erosive oesophagitis. Lastly, the efficacy of treatment and the medication safety profiles over a prolonged period of time were not examined.

There are several strengths in this meta-analysis. We included only randomized, placebo-controlled trials, thus ensuring a minimum standard of quality. Each individual trial was critically evaluated by the Jadad scoring system; the mean Jadad score was about 3.5, indicating a relatively high quality of the included trials. The funnel plots suggested the presence of a small study effect, which may indicate publication bias. Unfortunately, because of the relatively small number of trials for each specific clinical outcome, the publication bias could not be corrected.[20] Lastly, we performed heterogeneity tests for all analyses; all of the chi-squared calculations had a *P*-value of 0.1 or above (mean $P = 0.5$), suggesting the absence of significant heterogeneity. All I^2 calculations had values <50%, further confirming the relative homogeneity among the trials.

Overall, in this meta-analysis, several OTC therapies have been shown to be efficacious in prevention and

treatment of GERD symptoms. H2RAs, antacids, and alginate/antacid combinations are likely to continue to play a significant role in the treatment of GERD.

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REFERENCES

1 The Gallup Organization. *A Gallup Organization National Survey: Heartburn Across America*. Princeton, NJ: Gallup Organization, 1988.
2 Jadad AR, Moore RA, Carroll D, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.
3 Ciociola AA, Pappa KA, Sirgo MA. Nonprescription doses of ranitidine are effective in the relief of episodic heartburn. *Am J Ther* 2001; **8**: 399–408.
4 Paul K, Redman CM, Chen M. Effectiveness and safety of nizatidine, 75 mg, for the relief of episodic heartburn. *Aliment Pharmacol Ther* 2001; **15**: 1571–7.
5 Chatfield S. A comparison of the efficacy of the alginate preparation, Gaviscon Advance, with placebo in the treatment of gastro-oesophageal reflux disease. *Curr Med Res Opin* 1999; **15**: 152–9.
6 Pappa KA, Williams BO, Payne JE, Buaron KS, Mussari KL, Ciociola AA. A double-blind, placebo-controlled study of the efficacy and safety of non-prescription ranitidine 75 mg in the prevention of meal-induced heartburn. *Aliment Pharmacol Ther* 1999; **13**: 467–73.
7 Pappa KA, Gooch WM, Buaron K, *et al*. Low-dose ranitidine for the relief of heartburn. *Aliment Pharmacol Ther* 1999; **13**: 459–65.
8 Galmiche JP, Shi G, Simon B, Casset-Semanza F, Slama A. On-demand treatment of gastro-oesophageal reflux symptoms: a comparison of ranitidine 75 mg with cimetidine 200 mg or placebo. *Aliment Pharmacol Ther* 1998; **12**: 909–17.
9 Spiegel JE, Thoden WR, Pappas K, Fratarcangelo P, Furey SA. A double-blind, placebo-controlled study of the effectiveness and safety of nizatidine in the prevention of postprandial heartburn. *Arch Intern Med* 1997; **157**: 1594–9.
10 Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. *Scand J Gastroenterol* 1989; **24**: 401–6.
11 Beeley M, Warner JO. Medical treatment of symptomatic hiatus hernia with low-density compounds. *Curr Med Res Opin* 1972; **1**: 63–9.
12 Lanza FL, Smith V, Page-Castell JA, Castell DO. Effectiveness of foaming antacid in relieving induced heartburn. *South Med J* 1986; **79**: 327–30.
13 Stanciu C, Bennett JR. Alginate-antacid in the reduction of gastro-oesophageal reflux. *Lancet* 1974; **1**: 109–11.
14 Simon TJ, Berlin RG, Gardner AH, Stauffer LA, Gould AL, Getson AJ. Self-directed treatment of intermittent heartburn: a randomized, multicenter, double-blind, placebo-controlled evaluation of antacid and low doses of an H (2)-receptor antagonist (famotidine). *Am J Ther* 1995; **2**: 304–13.
15 Pappa KA, Buaron KS, Mandich M, *et al*. A double-masked, placebo-controlled study of the efficacy and safety of premeal ranitidine in the prevention or reduction of heartburn. *Curr Ther Res* 1998; **59**: 454–66.
16 Korn SH, Murakami A, Stauffer LA, Tipping RW. *A Controlled Comparison of Symptom Relief Provided by a Famotidine/Antacid Combination Tablet for the Treatment of Frequent Heartburn*. Data on file of Merck Research Laboratories, New Jersey, USA.
17 Koelz HR. Treatment of reflux esophagitis with H2-blockers, antacids and prokinetic drugs. An analysis of randomized clinical trials. *Scand J Gastroenterol* 1989; **156**: 0S25–36.
18 Stalnikowicz-Darvasi R. H2 antagonists in the treatment of reflux esophagitis: a critical analysis. *Am J Gastroenterol* 1989; **84**: 245–8.
19 Graham DY, Patterson DJ. Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitis. *Dig Dis Sci* 1983; **28**: 559–66.
20 Kaizar EE. Metaanalyses are observational studies: How lack of randomization impacts analysis. *Am J Gastroenterol* 2005; **100**: 1233–6.