Table S1. Summary of Studies Identified in Review of Published Literature on Interventions for Nocturnal Occasional and Frequent Heartburn

Reference	Design	Intervention(s)	**Objective Sleep Results**	**Subjective Sleep Results**
Aimi 2014	RCT	Omeprazole vs placebo taken 30 min before dinner 1/day for 2 weeks	Not discussed or mentioned	ESS, PSQI, diary record of sleep quality - Total QOLRAD-J score significantly improved in the omeprazole group 3.4% vs placebo group 1.5% - QOLRAD-J sleep-related score significantly improved by omeprazole 4.7% vs placebo 3.1% - Similar effects on ESS, PSQI, and sleep diary records
Allampati 2017	Open-label or non-RCTs	Positional therapy device (PTD)	Not discussed or mentioned	> Significant improvement from baseline with PTD by GERD-HRQL questionnaire (29.8–16.7, p<0.001) > In N-GSSIQ questionnaire, questions about sleep: - Have trouble falling asleep because of your heartburn/reflux? (p<0.001) -- Baseline: 2.8 ± 1.3 -- Post survey: 0.88 ± 1.3 - Wake up at night because of your heartburn/reflux? (p<0.001) -- Baseline: 3.1 ± 1.3 -- Post-survey: 0.76 ± 1.01
Aly 2010	RCT	conventional esophagectomy	Not discussed or mentioned	Records of sleep disturbances, modifications to sleeping arrangements, and sleep disturbance due to reflux > Significant reduction in incidence of sleep disturbance due to reflux in

				fundoplication vs anastomosis group > This impact was moderate or severe in 40% of the standard anastomosis group vs 5% in fundoplication group (p=0.01) Incidence of sleep disturbance due to reflux, % > 3 months, p=0.2 - Wrap: 17% - Standard: 50% > 6 months, p=0.01 - Wrap: 15% - Standard: 65% > 12 months, p=0.005 - Wrap: 25% - Standard: 82%
Cadiot 2008	Conference abstract	PPI alone or plus other treatments 1 month	Not discussed or mentioned	Questionnaire on symptomatic evaluation with 4 sleep rating scales (time taken to fall asleep, duration of sleep, quality of sleep and morning sleepiness) carried out by the physician before treatment and by the patient before and after treatment > Significant reduction in frequency and intensity of nocturnal symptoms at 1 mo > 4 sleep rating scales (time taken to fall asleep, duration of sleep, quality of sleep and morning sleepiness) significantly improved with treatment > Night awakenings decreased from

				89% to 18% and the mean number of nights with interrupted sleep decreased from 3.8 to 1.8 per week
Chand 2004	Open-label or non-RCTs	Esomeprazole 40 mg once daily 30 to 60 min before breakfast for 8 weeks (started on Day 2)	Objective assessment of sleep via wrist actigraphy watch worn continuously for 48 h generating activity record: sleep efficiency, immobility time percentage, and total activity. > No statistically significant differences in actigraphy watch measurements (median sleep efficiency, immobile time percentage and total activity score) over time > No statistically significant difference in the proportions of normal scores for sleep efficiency of baseline vs week 4 or 8	GSRS, PSQI > Median global PSQI score decreased significantly with esomeprazole, 8.50 (IQR: 6.0- 11.0) at baseline to 4.50 (IQR: 4.0-11.0) at week 4 (p=0.008) and to 7.0 (IQR: 4.0-9.0) at week 8 (p<0.05) > # with normal global PSQI score was 11.1% at baseline and increased significantly to 50.0% at week 4 (p<0.01) and 27.8% at week 8 (p<0.05) > Global reflux syndrome and PSQI score no significant correlation
Chen 2006	Conference abstract	Esomeprazole 40 mg orally once daily for 8 weeks	Not discussed or mentioned	Global PSQI > global PSQI score decreased from 5.0 at baseline to 3.6 at week 8 (p<0.01). > Significant improvement in subjective sleep in mild esophagitis (p=0.03)
Chey 2008	Conference abstract	Rx PPI (drug not specified)	Not discussed or mentioned	WPAI-GERD > Patients with nighttime symptoms were more likely to go to bed later than they would like (20.1% vs. 4.0%, p=0.006) > Among patients with nighttime

				symptoms who reported having problems sleeping at night, 97% experienced problems on ≥ 1 night during past 30 days. > Most commonly sleep problems: "waking up at night" (66.2%), "trouble falling asleep again after waking up" (52.6%), and "trouble falling asleep" (37.2%) > The risk of sleep difficulty increased with nighttime symptom severity: OR=3.88 (p=0.012) for moderate severity, and 13.95 (p=0.006) for severe/very severe, compared to those with slight severity
Cihang 2022 [40]	RCT	4 diet intervention groups for a period of 9 weeks: - High total/high simple carbohydrate (HTHS) - High total/low simple carbohydrate (HTLS) - Low total/high simple carbohydrate (LTHS) - Low total/low simple	Not discussed or mentioned	GERDQ > Changes in GERDQ sleep factor by diet treatment arm: - HTHS (High-total/high simple carbohydrates), means±SD: -0.1±1.0, p=N.S. - HTLS (High-total/low-simple carbohydrates), means±SD: -0.5±1.4, p<0.05 - LTHS (low-total/high-simple carbohydrates), means±SD: -0.7±0.9, p<0.01 - LTLS (low-total/low-simple carbohydrates), means±SD: -0.5±0.9, p<0.05 > Average total GERDQ score ratings reduced by 19% in the HTHS group, 50% in the HTLS group, 46% in the

		carbohydrate (LTLS) diet		LTHS group, and 50% in the LTLS group. > Average total GSAS score ratings reduced by 42% in the HTHS group, 52% in the HTLS group, 38% in the LTHS group, and 53% in the LTLS group. > The improvements in GERDQ and GSAS scores were not statistically different for subjects with "pathologic" vs "inconclusive" GERD in any of the diet groups
Clayton 2011	Conference abstract	Twice daily PPI (drug not specified)	Multichannel Intraluminal Impedance with-pH (MII-pH) The nocturnal recumbent period (the period documented by patients during which they lie in the recumbent period at night to sleep) - average periods lasting 456 and 453 minutes for patients on and off PPI therapy, respectively	Not discussed or mentioned
DeVault 2006	Conference abstract	Pantoprazole 40 mg vs esomeprazole 40 mg 1/day for 4 weeks	Not discussed or mentioned	ReQuest™ > Both regimens increased rate of 'good' sleep with significantly higher proportion in the pantoprazole group ($p<0.0001$) vs the esomeprazole group > statistically significant superiority of pantoprazole versus esomeprazole ($p=0.012$) for good sleep

Dewan 2011	Conference abstract	PPI for 4 weeks (drug not specified)	Not discussed or mentioned	SHHS, Trail making test, Digit span test, MMSE > After 4 weeks of PPI therapy, symptom-related awakenings improved significantly (p<0.005)
DiManno 2004	Conference abstract	Omeprazole 20 mg orally 2/day for 2 weeks	Nocturnal polysomnographic with simultaneous esophageal pH monitoring > Total sleep time (mean +/- SE) increased from 294.0 +/- 15.9 minutes to 345.6 +/- 55.6 minutes (p<0.05). > Total awake time decreased from 99.1 +/- 17.9 minutes to 46.1 +/- 15.3 minutes (p<0.05). > Sleep efficiency improved from 70.2% to 81.6% (p<0.05). > REM sleep time improved from 55.0 +/- 4.5 minutes to 94.5 +/- 18.9 minutes (p<0.05). > Number of awakenings decreased from 8.7 +/- 2.0 minutes to 3.2 +/- 0.7 minutes (p<0.01). > Time in other sleep stages, including 1,2, and delta (3 and 4), did not change and sleep latency decreased and degree of daytime refreshment after treatment with omeprazole improved but these changes were not significant (p>0.05)	Not discussed or mentioned
Donnelly 2003	Conference abstract	omeprazole 20 mg morning dose with placebo	Not discussed or mentioned	Statistically significantly less interference with sleep by ranitidine and omeprazole vs. placebo (p<0.05)

		before evening provocative meal, or placebo morning dose with evening ranitidine 75 mg prior to the meal, or placebo morning and evening.		- 33% of subjects on placebo had no sleep interference compared with 58% for ranitidine and 50% for omeprazole.
Fass 2004	Conference abstract	Esomeprazole 40 mg orally 1/day for 4 weeks	Sleep study (not specified in abstract) > The sleep study revealed a significant increase in sleep period time (376 + 22.7 vs. 410 + 8.9 min) and total sleep time (338 + 13.4 vs. 384 + 39.7) as well as a significant reduction in totalnumber of arousals (133 + 20 vs. 118.6 + 14.3) (all p<0.01) in patients treated with Esomeprazole	Sleep habits questionnaires and short form (SF)-36 > Patients receiving esomeprazole reported significant reduction in the number of naps needed per day, having trouble falling asleep, waking up during the night, feeling over-sleep), during the day and taking sleeping pills (all p<0.05). > Treated pts with esomeprazole also reported a significant reduction in snoring (p<0.05).
Fass 2011 [32]	RCT	Dexlansoprazole MR 30 mg vs placebo given orally 1/day in morning for 4 weeks.	Not discussed or mentioned	Daily diary entries, PSQI Daily diary entries > A significantly greater percentage of patients in the dexlansoprazole MR 30 mg group vs placebo group reported relief of nocturnal heartburn or GERD-related sleep disturbances (47.5 vs. 19.6% and 69.7 vs. 47.9%, respectively; p<0.001 for both

				variables). > Patients receiving dexlansoprazole MR reported a significantly lower percentage of nights with sleep disturbance due to GERD compared with placebo (median of 11.1 vs. 36.8%; p<0.001). > Patients in dexlansoprazole MR group experienced significantly fewer nights with each specific GERD-related sleep disturbance (p<0.001) and significantly fewer mornings impacted by sleep disturbances (p<0.001). PSQI: > Improvements from baseline to week 4 in sleep quality by PSQI significantly greater in the dexlansoprazole MR 30 mg group vs. the placebo group (mean of −2.70 vs. −1.35; p=0.001).
Fujiwara 2013 [54]	Cohort	Rabeprazole 10 mg orally 2/day for 4-8 weeks	Not discussed or mentioned	Questionnaire on sleep disturbances includes 4 questions regarding nighttime symptoms, arousals during sleep due to nighttime symptoms, daytime sleepiness, and sleep quality > rabeprazole treatment significantly ameliorated nighttime symptoms, arousals during sleep, and daytime sleepiness (p<0.01) > 58.7% assessed their sleep quality as very good, good, or moderate

				before treatment, while such sleep quality was found in 85.3% after treatment, suggesting rabeprazole treatment significantly improved sleep quality
Fujiwara 2010 [54]	Open-label or non-RCTs	Rabeprazole 10 mg 1/day for 8 weeks	Not discussed or mentioned	FSSG questionnaire, PSQI > The FSSG score in patients with sleep dysfunction significantly higher vs without sleep dysfunction (p=0.0347) suggesting GERD symptom frequency is positively associated with severity of sleep quality and quantity > Rabeprazole significantly decreased global PSQI score compared to baseline (p=0.0032) > Significant reduction in scores on sub-analysis: - subjective sleep quality (p=0.02) - sleep disturbance (p=0.04) - not significant in other measures (sleep latency, sleep duration, habitual sleep efficacy, use of sleeping medication, daytime dysfunction)
Gagliardi 2009 [41]	Cross-over	Zolpidem tartrate 10 mg vs placebo; single dose given approximately 30 minutes prior to bedtime.	Overnight polysomnography - Reflux-related arousals and awakenings: events with no other identifiable source that occurred during the acid reflux event and up to 5 minutes after the pH return to >4.0. Reflux-associated arousals	Not discussed or mentioned

			> Among all 23 subjects (controls and GER), a nocturnal acid reflux event led to arousal or awakening 89% of the time with placebo vs 40% with zolpidem ($p<0.01$) > Absence of arousal response was noted in the first part of evening (first 3 hours post zolpidem) with intact arousal response prior to morning awakening. - The arousal response was present in both groups regardless of the duration of acid exposure suppressed by zolpidem.	
Gerson 2009 [3]	Systematic review	> Fundoplication > PPI: Esomeprazole 40 mg, 20 mg - Rabeprazole 20 mg 30 min before breakfast or dinner - Immediate-release omeprazole (IR-OME) - Lansoprazole > H2RAs - Ranitidine > HOB elevation > Right lateral decubitus position	Not discussed or mentioned	Not discussed or mentioned

Giannini 2008	Open-label or non-RCTs	> Empirical approach, group 1: 40 mg esomeprazole once daily > group 2: Basal endoscopy - Esophagitis LA grade A-D treated with 40 mg esomeprazole once daily - NERD treated with 20 mg esomeprazole once daily > Patients in any treatment group free from symptoms following 4 weeks of treatment were treated for a further 20 weeks with esomeprazole 20 mg once daily maintenance therapy	Not discussed or mentioned	QOLRAD Mean dimension score for sleep > At baseline - Group 1: 4.3 ± 1.4 - Group 2: 4.4 ± 1.4 > At the end of acute phase - Both group: 6.1 ± 1.0 > At the end of maintenance phase - Group 1: 6.6 ± 0.8 - Group 2: 6.5 ± 0.9 *Analysis of covariance performed with baseline value as covariate to compare treatment groups showed no statistically significant difference.
Guda 2007	Cross sectional	> PPI (n=19), H2RA (n=7), combination (n=1) *Did not specify	Not discussed or mentioned	ESS > Mean ESS in patients with GERD (12.88±5.5) was significantly

		dosage and frequency		(p=0.007) higher vs without GERD (10.6±4.9)
Gunasekaran 2009	RCT	> Esomeprazole 20 or 40 mg 1/day for 8 weeks	Not discussed or mentioned	QOLRAD > QOLRAD mean total scores and all mean domain scores (including sleep dysfunction) were improved significantly from baseline (p<.001)
Hansen 2006	RCT	> Symptom-control phase: Esomeprazole 40 mg 1/day for 4 weeks > Follow-up phase for patients relieved of symptoms - Esomeprazole 20 mg given as maintenance 1/day for 6 mo - Esomeprazole 20 mg given on-demand for 6 mo - Ranitidine 150 mg given as maintenance 2/day for 6 mo	Not discussed or mentioned	QOLRAD questionnaire, sleep disturbance dimension > Mean change in QOLRAD scores from visit 2 to final visit showed continuous and on-demand esomeprazole were significantly superior to ranitidine continuously in maintaining QoL (p<0.0001 for sleep disturbance). - Clinically relevant with difference of ≥0.5 on the Likert scale > Esomeprazole continuously significantly more effective at maintaining a high QOLRAD score vs esomeprazole on-demand for sleep disturbance QOLRAD dimension - % patients suffering from sleep disturbance 'at least some of the time', baseline vs following treatment: 94.5 vs 22.5
Hawkey 2007	RCT	> Esomeprazole 40 mg vs 20 mg vs placebo 1/day for 6 mo	Not discussed or mentioned	QOLRAD, sleep disturbance dimension > At 6 mo, esomeprazole 20 and 40 mg were significantly more effective

				vs placebo for maintaining improvements in HRQL by mean changes in QOLRAD questionnaire sleep disturbance dimension (esomeprazole 20 mg: p=0.02, esomeprazole 40 mg: p=0.005).
Hawkey 2003	Conference abstract	> Esomeprazole 40 mg vs 20 mg 1/day for 4 weeks.	Not discussed or mentioned	QOLRAD, sleep dysfunction dimension > Esomeprazole significantly improved HRQL of life on the QOLRAD QOLRAD scores > Sleep dysfunction - Esomeprazole 40 mg: 1.43, p≤0.01 vs placebo - Esomeprazole 20 mg: 1.54, p≤0.01 vs placebo - Placebo: 1.09
Hayashi 2013	Conference abstract	Rabeprazole given 2/day	Not discussed or mentioned	Self-reporting questionnaire with 4 questions about sleep: Nighttime reflux symptoms, arousal due to reflux symptoms, daytime sleepiness, sleep quality > Scores for sleep disturbance were significantly higher in PPI-refractory patients vs reporting successful treatment (FSSG <8) > Nighttime reflux symptoms (score >1) decreased from 71% to 18%, arousal due to reflux symptom (score >1) decreased from 48% to 20%, daytime sleepiness (score >1)

				from 36% to 15%, and bad or very bad sleep quality (score >3) from 42% to 12% (all p<0.0001)
Hiramoto 2015	Open-label or non-RCTs	Esomeprazole 20 mg given 1/day for 2 weeks	Sleep actigraphy > Esomeprazole treatment significantly decreased total wake time but not affect # of awake episodes. > % of sleep after first and second week of esomeprazole treatment was significantly higher vs before treatment, especially among patients whose % sleep values exhibited an improvement of <95%. - After first week: p=0.019 - After second week: p=0.013 > Compared to before treatment, sleep latency at second week of esomeprazole demonstrated a significant decrease (p=0.016). > Although esomeprazole did not lead to improvements in all objective sleep parameters, several parameters, in addition to those described above, showed improvements after the treatment	PSQI, ESS > Esomeprazole did not affect the total PSQI score > ESS score significantly decreased from 4.8±1.1 before treatment to 3.8±1.0 after treatment (p<0.05), suggesting 2 weeks of esomeprazole had little effect on subjective sleep parameters
Hunt 2009	Conference abstract	> Esomeprazole 20 mg or 40 mg given 1/day for 4 weeks	Not discussed or mentioned	PASS Test question: Is your sleep affected by your stomach symptoms? > OR for PASS test with intervention vs control was 0.30 (95% CI: 0.21 to 0.42; p<0.0001), indicating significant

				reduction in sleep disturbance following a switch to esomeprazole. Sleep disturbance in each group > Baseline - Intervention group ('I'): 586 (60%) - Control centers ('C'): 353 (60%) > Week 4 - Intervention group ('I'): 246 (25%) - Control centers ('C'): 315 (53%)
Ing 2000	Cross sectional	> Nizatidine 150 mg vs placebo 2/day for 1 month	Polysomnographic studies > Arousal index significantly reduced with nizatidine > Comparing posttreatment parameters between the 2 groups, active medication group had significantly fewer arousals.	Not discussed or mentioned
Jha 2016 [42]	RCT	> Ramelteon 8 mg vs placebo given 1/day before bed time for 4 weeks. > Placebo given	Actigraphy Results not discussed or mentioned.	SSI questionnaire, PSQI > SSI score significantly reduced with ramelteon (pre 14.5±1.83 vs. post 7.88±1.8) vs placebo (pre 12.63±1.94 vs. post 12.0±2.6) (−46% vs. −5%; $p<0.05$). > ramelteon group demonstrated significant improvement in sleep latency, total duration of awakening, and estimated amount of sleep per patient vs placebo, $p<0.05$.
Jha 2012	Conference abstract	Esomeprazole 40 mg 1/day for 7 days.	Actigraphy > mean # conscious awakenings with	Not discussed or mentioned

			acid reflux event was significantly lower after treatment with esomeprazole compared to baseline (2+2.1 min vs 1+1.5 min, p=0.02). > no statistically significant difference in mean duration of recumbent awake period, and mean # and duration of conscious awakenings from sleep during treatment as compared to baseline.	
Jha 2015	Cohort	Esomeprazole 40 mg 1/day for 7 days	Actigraphy > esomeprazole had no impact on total # and duration of conscious awakenings. - Antireflux treatment may shorten the duration of a conscious awakening that is associated with acid reflux, although the results did not quite reach statistical significance (p=0.07). > Characteristics of conscious awakenings during sleep and their relationship with acid reflux events, pre-treatment vs. after treatment (mean ±SD) - Mean total number of conscious awakenings (4.7±3.26 vs. 5.10±3.39, p=0.6458) - Mean total number of conscious awakenings with acid reflux event (2±2.05 vs. 1±1.49 p=0.0197)	Not discussed or mentioned

			> Characteristics of conscious awakenings during sleep and their relationship with acid reflux events before and at the end of 7 day treatment with esomeprazole 40 mg once daily (mean ±SD). - Mean duration of conscious awakening (min): 75.9±66.47 vs 91.94±75.18 (p=0.4480) - Mean duration of conscious awakening with acid reflux event (min): 50.45 ± 60.80 vs. 20.68 ± 40.34 (p=0.0740) - Mean duration of conscious awakening with acid reflux event and GERD-related symptoms (min): 5.95±16.36 vs. 0.68±2.98 (p=0.1222) - Mean Sleep Time (min): 378.9±117.178 vs. 423±106.466 (p=0.1199)	
Johannessen 2012	Cross sectional	> Laparoscopic funduplication > Open fundoplication	Not discussed or mentioned	RASQ > Sleeplessness scores: not significantly different, although tendency toward lower scores in operated patients. RASQ Sleeplessness Scores between operated and non-operated patients, p=NS > Operated patients: - Median (IQR): 1 (0–3) - Mean: 1.45 > Non-operated patients:

				- Median (IQR): 2 (1–3) - Mean: 1.79
Johnson 2010 [31]	RCT	> Esomeprazole 20 mg vs placebo 1/day before breakfast for 4 weeks.	Not discussed or mentioned	PSQI, WPAI-SLEEP-GERD > Relief of GERD-related sleep disturbance was significantly (p=0.006) more in esomeprazole group vs placebo group during last 7 days of the study. > esomeprazole resulted in significantly (p=0.0003) more days without GERD-related sleep disturbances vs placebo group. > Complete resolution of GERD-related sleep disturbances during last 7 days of the study significantly more (p<0.0001) in the esomeprazole group (48.2%) vs placebo group (21.6%). > Resolution of sleep disturbances faster with esomeprazole, with median of 9 days to the first complete resolution of sleep disturbance > More patients treated with esomeprazole 20 mg had good sleep (PSQI≤5) or sleep disturbances (PSQI >5) at baseline experienced good sleep after 4 weeks vs placebo, although difference did not reach statistical significance (p=0.07). > Employed patients who received esomeprazole (n=83) reported significantly larger change in overall work hours lost from baseline to end of study attributed to GERD-related

				sleep disturbances (-9.5 vs. -4.9 h) vs placebo (n=78). - Least square means (LSM) difference, −4.64; 95% CI: −7.2 to −2.1; p=0.0005 > The impact of GERD-related sleep disturbances on work productivity was significantly lower in esomeprazole group (n=83) vs placebo group (n=78). - LSM difference, −1.24; 95% CI: −1.9 to −0.6; p=0.0002
Johnson 2010 [31]	Conference abstract	Esomeprazole 40 mg 1/day in morning for 4 weeks	Not discussed or mentioned	ESS > Overall average % nights with sleep disorder were reduced (62.5% vs. 9.5%; p<0.001). > ESS decreased to 5.9±3.5 from 7.9±2.5 (p=0.056).
Johnson 2009	Conference abstract	> Esomeprazole 20 mg vs placebo 1/day (before breakfast) for 4 weeks.	Not discussed or mentioned	PSQI > Improvements in sleep quality significantly greater after 4 weeks of esomeprazole treatment vs placebo (p=0.03). PSQI scores > Mean PSQI baseline score: - Esomeprazole: 9.4 - Placebo: 8.8 > Mean PSQI week 4 score: - Esomeprazole: 6.3 - Placebo: 7.0 > Least square mean change in PSQI

				score from baseline (95% CI), p=0.003: - Esomeprazole: −2.9 (−3.6, −2.3) - Placebo: −1.8 (−2.5, −1.1) > Good sleep at week 4 (baseline PSQI ≤5), n/N (%): - Esomeprazole: 19/21 (90.5%) - Placebo: 24/29 (82.8%) > Good sleep at week 4 (baseline PSQI >5), n/N (%): - Esomeprazole: 50/113 (44.2%) - Placebo: 31/94 (33.0%)
Johnson 2009	Conference abstract	> Esomeprazole 20 mg vs placebo 1/day (before breakfast) for 4 weeks.	Not discussed or mentioned	WPAI-SLEEP-GERD Least-squares mean changes in WPAI-SLEEP-GERD end points after 4 weeks (esomeprazole vs placebo) > Sleep disturbance affected work productivity, p<0.001 - Esomeprazole: −2.7 - Placebo: −1.4 - 95% CI: −1.2 (−1.9, −0.6) > Sleep disturbance affected regular activities, p=0.003 - Esomeprazole: −2.7 - Placebo: −1.7 - 95% CI: −1.0 (−1.7, −0.3)
Johnson 2009	Conference abstract	> Esomeprazole 20 mg vs placebo 1/day for 4 weeks.	Not discussed or mentioned	Daily diary card, complete resolution of sleep disturbance (7 consecutive days of no trouble sleeping the previous night) > Median 9 days to first complete resolution of sleep disturbance with

				esomeprazole, whereas the majority of patients (>50%) who received placebo never experienced complete resolution (p=0.0001). > % relief of GERD related sleep disturbance after 4 weeks, p<0.01 - Esomeprazole: 71.5% - Placebo: 55.2%
Johnson 2015 [17]	Other clinical studies (specify)	> Esomeprazole 20 mg vs placebo given 1/day 30-60 min before breakfast for 4 weeks.	Not discussed or mentioned	> Daily self-assessment diary - Occurrence of GERD-related sleep disturbances during first 2 weeks of treatment with esomeprazole 20 mg or placebo. - Complete resolution of GERD-related sleep disturbance: no sleep disturbance on 7 consecutive days. - Relief of GERD-related sleep disturbance: sleep disturbance on ≤2 of 7 days. - Time to first resolution of GERD-related sleep disturbance: defined as the first day on which daily diary response regarding the occurrence of sleep disturbances was 'no'. > The occurrence of GERD-related sleep disturbances and frequency and severity of heartburn episodes were recorded by subjects in a daily self-assessment diary > Sleep quality at baseline and week 4 by the PSQI questionnaire > WPAI questionnaire

				Subjective sleep results: > significant effect of active treatment in proportion of subjects who achieved complete resolution and relief of GERD-related sleep disturbances at weeks 1 and 2 in trial 1 and trial 2. > Esomeprazole 20 mg provided rapid resolution of sleep disturbances, with significant difference between the curves of time to first resolution of sleep disturbance across days 1 to 14 of treatment between esomeprazole and placebo in trial 1 ($p<0.0001$; log-rank test) and trial 2 ($p<0.0056$; log rank test). Median time to first resolution of GERD-related sleep disturbance: > Esomeprazole 20 mg vs placebo - Trial 1: 1 day vs 3 days; $p<0.0001$ on log-rank test - Trial 2: 1 day vs 2 days; $p=0.0106$ on log-rank test > >50% of subjects in esomeprazole group had no sleep disturbance on the first night of treatment. Resolution of GERD-related sleep disturbances within the first 2 days > A higher cumulative % subjects in the esomeprazole group vs placebo group achieved first resolution of GERD-related sleep disturbances

				within the first 2 days. > Esomeprazole vs placebo group, % (CI) - Trial 1: 76.8% (95% CI: 71.2%–82.4%) vs 48.4% (95% CI: 41.8%–55.0%); p<0.0001 - Trial 2: 81.1% (95% CI: 74.5%–87.6%) vs 64.8% (95% CI: 56.4%–73.2%); p=0.003
Johnson 2014	Conference abstract	> Esomeprazole 20mg vs placebo 1/day for 4 weeks* * Only data from the first 14 days were utilized in this report.	Not discussed or mentioned	Daily self-assessment diary > A significantly higher proportion of subjects treated with esomeprazole 20 mg had relief/resolution of GERD-related sleep disturbances in weeks 1 and 2 of treatment. Efficacy outcomes with 14-day treatment with esomeprazole 20 mg or placebo > With complete resolution of GERD-related sleep disturbance (no sleep disturbance on 7 consecutive days), n(%) - Week 1: Esomeprazole vs placebo: 89 (40.5) vs 21 (9.5); p<0.0001 - Week 2: Esomeprazole vs placebo: 111 (50.2) vs 44 (19.9); p<0.0001 > Relief of GERD-related sleep disturbance, n (%) - Week 1 Esomeprazole vs placebo: 157 (71.4) vs 99 (44.8); p<0.0001 - Week 2 Esomeprazole vs placebo: 174 (79.1) vs 111 (50.2); p<0.001

				> Time to first resolution of GERD-related sleep disturbance, n (%) - Week 1 Esomeprazole vs placebo: 158 (71.8) vs 98 (44.3); p<0.0001 - Week 2 Esomeprazole vs placebo: 169 (76.8) vs 107 (48.4); p<0.001
Johnson 2005 [19]	RCT	> Esomeprazole 20 mg vs 40 mg vs placebo once daily 30 minutes before breakfast for 4 weeks. * Not more than 6 antacids tablets per day or 21 tablets over any 7-day period were allowed as rescue medication for acute GERD symptoms	Not discussed or mentioned	Symptom diary card, PSQI, WPAI-SLEEP-GERD > Complete resolution and relief of GERD-associated sleep disturbances were similar in the esomeprazole 40- and 20-mg groups, and significantly higher (p<0.0001) in both groups vs placebo group. > Mean (SD) % of days without sleep disturbances during the study, both p<0.0001 vs placebo group: - Esomeprazole 40 mg group: 83.2 (22.3)% - Esomeprazole 20 mg group: 84.1(19.0)% - Placebo group: 61.5 (28.6)% PSQI: > At baseline, 527/632 (83%) of patients had poor sleep quality; by week 4, 111/204 (54%) patients treated with esomeprazole 40 mg and 91/214 (43%) treated with esomeprazole 20 mg had poor sleep quality vs 137/214 (64%) patients receiving placebo (p<0.001). > The least square mean (LSM)

				changes from baseline to week 4 in global PSQI score were not statistically significant between the esomeprazole group (40 mg, −3.64 vs 20 mg, −4.00), with both improvements significantly greater vs placebo group (−2.19, p<0.0001). WPAI-SLEEP-GERD > The degree to which sleep disturbance affected both work productivity and regular activities was significantly more reduced in the esomeprazole groups (p<0.001) vs placebo group.
Katz 2014	Conference abstract	> Magnetic sphincter augmentation device (MSAD) implanted during laparoscopic procedure. > PPI (drug and regimen not specified)	Not discussed or mentioned	GERD-HRQL > Heartburn waking patients from their sleep nightly was 1% off PPIs (after surgery) versus 14% on PPIs (p=0.004). Comparison Between Baseline On PPIs and Post-MSAD Off PPIs: > Median total GERD-HRQL score: 11 vs 4, p<0.0001 > Median GERD-HRQL score for heartburn questions: 8 vs 3, p<0.0001 > % of patients waking nightly with heartburn: 14 vs 1, p=0.004 > % of patients satisfi ed with their present condition: 13 vs. 84, p<0.0001
Kawai 2017	RCT	> Either rabeprazole 20	Not discussed or mentioned	QOL, RESQ

		mg/day (n=20), lansoprazole (LPZ) 30 mg/day (n=18), or omeprazole 20 mg/day (n=9)] for ≥8 weeks > continued PPI with addition of rikkunshito (7.5 g thrice a day) for 6-8 weeks		QOL score was surveyed using the RESQ > Difficulty falling asleep - Pre-treatment: 2.81 ± 0.80 - Post-treatment: 2.83 ± 0.82 - p=0.563 > Interrupted sleep - Pre-treatment: 2.64 ± 0.76 - Post-treatment: 2.81 ± 0.71 - p=0.035
Kawami 2022	Open-label or non-RCTs	> Rikkunshito 7.5 g 1/day for 8 weeks	Not discussed or mentioned	QOLRAD-J > Total score and scores for emotional distress, sleep disturbance, eating/drinking disorders, physical/social functioning, and vitality were higher at 8 weeks after treatment or at discontinuation than before treatment. > No significant differences observed (before treatment vs. 8 weeks after treatment or at discontinuation) > Total: 5.26 ± 1.12 vs. 5.61 ± 1.16, p=0.264 > Sleep disturbance: 5.40 ± 1.33 vs. 5.58 ± 1.49, p=0.797 > Emotional distress: 4.60 ± 1.63 vs. 5.17 ± 1.81, p=0.234 > Eating/drinking disorders: 5.40 ± 1.24 vs. 5.72 ± 1.04, p=0.299 > Physical/social functioning: 5.80 ± 0.93 vs. 6.10 ± 0.94, p=0.164

				> Vitality: 5.13 ± 1.36 vs. 5.53 ± 1.43, p=0.320
Khan 2012	Cohort	> Bed head elevation by raising entire bed frame on wooden block of 20cm height, the head end	Not discussed or mentioned	Diary card recording symptom as complete resolution of sleep disturbance (no response on 7 consecutive days) and relief of sleep disturbance (no more than 2 of 7 consecutive days) > 13 of 20 (65%) patients reported improvement in sleep disturbance
Kim 2023	RCT	> tegoprazan 50 mg daily with placebo or esomeprazole 40 mg with placebo for 2 weeks > advised to take medication before bedtime > Antacids permitted daily with persistent symptoms despite medication	Not discussed or mentioned	Korean version of the Epworth sleepiness scale (KESS) > KESS score also improved in the tegoprazan group for both FAS (-1.2 vs 0.5, p=0.351) and PPS group (-1.2 vs -0.5, p=0.356), but did not reach statistical significance.
Kindt 2011	Cohort	> pantoprazole, dosage was according to physician's discretion - 94.4% received 40 mg once a day - 3.2% received 20 mg once a day	Not discussed or mentioned	QOLRAD Distribution of answers to sleep-related questions before treatment > 72% reported typical reflux symptoms in supine position > 39.1% suffered from reflux symptoms disturbing their sleep

		- 2.4% received 40 mg twice a day		> 45.1% woke up because of reflux symptoms > 34.1% have morning fatigue > 47.4% also experienced reflux symptoms when waking up in the morning > 16.4% did not have any nighttime complains > 19.4% answered positively to all five questions Distribution of answers to sleep-related questions after treatment > 10.5% still complained of reflux symptoms when supine > 21.7% experienced typical reflux symptoms during sleep > 19.7% woke up because of reflux symptoms > 24.4% suffered from morning fatigue > 18.9% had typical symptoms at waking up
Kulig 2003	Cohort	> Non-erosive GERD received 20 mg/day of esomeprazole for 2 weeks > Erosive GERD received 40 mg/day esomeprazole for 2 weeks	Not discussed or mentioned	QOLRAD > At baseline, patients feel restricted because of sleep dysfunction > After treatment, significant improvement in overall QOLRAD score from 4.6 to 6.2 points. This change of 1.6 (95% CI, 1.54-1.61) on a 7-point Likert scale is generally considered a very important clinical change.

Laine 2002	Open-label or non-RCTs	> 14-day course of 2/day lansoprazole 30 mg, amoxicillin 1g, and clarithromycin 500 mg	Not discussed or mentioned	QOLRAD > QOLRAD score for sleep disturbances - Baseline: 5.20 ± 0.26 - 6-month: 5.25 ±0.27 *difference (95% CI): -0.05 (-0.50-0.48)
Lauritsen 2002	Conference abstract	> Esomeprazole 40 mg 1/day for 4-8 weeks	Not discussed or mentioned	QOLRAD > At baseline, QOLRAD showed 58% patients suffered from sleep dysfunction (difficulty getting good night's sleep) > At end treatment, % patients who reported QOLRAD as the ff: - Healed: n=1268, 91.6% - Unhealed: n=44, 3.2% - Unknown outcome: n=73, 5.3%
Leodolter 2003	Conference abstract	> With erosive GERD: Esomeprazole 40 mg 1/day for 4-8 weeks > Without erosive GERD: Esomeprazole 20 mg 1/day for 4-8 weeks	Not discussed or mentioned	QOLRAD > In both groups (endoscopy positive and negative GERD), significant improvement in perceptions of their sleep disorders after 2 weeks of treatment (p<0.0001, Bowker-Test)
López-Alvarenga 2014	Cohort	> Pantoprazole-Mg 40 mg orally 1/day for 28±2 days and instructed to take	Not discussed or mentioned	ReQuest in Practice > Mean symptom severity before vs after treatment - Sleep disturbances: 1.37 (0.02) vs

		20-30 min before breakfast		0.26 (0.01), p<0.0001 > Patient assessment with ReQuest in Practice - Sleep disturbances, p=0.059
Maiti 2011	RCT	> Rabeprazole 40 mg 1/day for 4 weeks (n=30) > Esomeprazole 40 mg 1/day for 4 weeks (n=30)	Not discussed or mentioned	QOLRAD > Improvement with rabeprazole was similar to esomeprazole over 1 mo - In rabeprazole group, % change in sleep disturbance (46.4%) was significantly different compared to esomeprazole group Change in QOLRAD scoring (1st vist vs 2nd visit) > Rabeprazole group - Sleep disturbance: 7.24±4.0 vs 10.6±4.9, p<0.001 - Overall scoring: 38.0±13.6 vs 53.7±14.4, p<0.001 > Esomeprazole group - Sleep disturbance: 8.69±5.8 vs 9.58±5.6, p=0.02 - Overall scoring: 34.5±13.4 vs 38.9±12.5, p<0.001
Mann 1995 [36]	RCT	> Famotidine 10 mg 1/day at 19.00 hours with 100 mL of water *1 hour later the meal was consumed	Not discussed or mentioned	On awakening the following morning, patients assigned scores from the same scale in answer to the question: 'How do you feel the test drug controlled your heartburn during the night?' Patients also rated global assessment of the interference heartburn produced when they were trying to settle to sleep.

				> Higher proportions of famotidine treated patients reported no interference and fewer needed antacids. The difference in mean score was statistically significant in favor of famotidine.
Masihi 2020	Conference abstract	> Randomized and blinded to 3 different diets (A, B, or C), instructions were given on acceptable use of anti-acid therapy - Diet A and C differed in types of carbohydrates recommended - Diet B focused on mindful eating	Not discussed or mentioned	NIH GI PROMIS > Sleep improved significantly between week 2 and 8 (p=0.013) with no change in use of rescue anti-acids - Baseline vs week 2: 1.25(1.0) vs 0.50(1.0), p=0.013 - Week 2 vs week 8: 1.13(1.3) vs 0.50(0.97), p=0.076
Mathias 2001	RCT	> Lansoprazole 15 mg or 30 mg 1/day or 8 weeks > Ranitidine 150 mg 2/day for 8 weeks	Not discussed or mentioned	HRQoL - 57-item, battery-style questionnaire contains both generic and GERD-targeted measures. >QoL Scale Scores (Mean ± SE): Problem with sleep > Baseline: - Ranitidine 150 mg: 52.89 ± 1.55 - Lansoprazole 15 mg: 53.63 ± 1.55; p=0.92 - Lansoprazole 30 mg: 51.97 ± 1.54; p=0.88 > Week 4

				- Ranitidine 150 mg: 75.39 ± 1.42 - Lansoprazole 15 mg: 79.21 ± 1.42; p=0.10 - Lansoprazole 30 mg: 78.92 ± 1.41; p= 0.14 > Week 8 - Ranitidine 150 mg: 78.06 ± 1.51 - Lansoprazole 15 mg: 82.04 ± 1.51; p=0.10 - Lansoprazole 30 mg: 81.75 ± 1.50; p=0.14 > From baseline to week 8, statistical significance between the LAN 30 mg and RAN 150 mg groups was approached for social restrictions (SR) (19.51 ± 1.28 vs 16.05 ± 1.29, respectively; p=0.068), and problems with sleep (PSL) (29.60 ± 1.68 vs 25.04 ± 1.68, respectively; p=0.092) > HRQoL Change Scores - Statistical significance between the LAN 30 and RAN 150 groups was approached for social restrictions (SR) (19.51 ± 1.28 vs 16.05 ± 1.29, respectively; p= 0.068), and problems with sleep (PSL) (29.60 ± 1.68 vs 25.04 ± 1.68, respectively; p=0.092)
Moayyedi 2013	Open-label or non-RCTs	> esomeprazole 20 mg or 40 mg once daily (dosage at the discretion of physician; 96%	Not discussed or mentioned	QOLRAD > The mean QOLRAD scores related to sleep were statistically significantly higher in the intervention group indicating a better QoL in the sleep

		prescribed 40 mg daily) for 4 weeks > Control groups continued previous therapy for 4 weeks - H2RA, PPI (except omeprazole) and antacids as prescribed by PCP; dose and frequency not specified		domain. QOLRAD sleep question score > Baseline - Intervention: 19.57±7.77 (n=534) - Control: 20.61±7.66 (n=291) > After treatment: - Intervention: 29.81±8.49 (n=490) - Contol: 24.90±6.92 (n=273)
Modolell 2011	Open-label or non-RCTs	> Pantoprazole 80 mg 1/day for at ≥1 month, followed by a 40 mg/day maintenance dose, for a total of 3–6 months	Polysomnography > 23 patients (20%) had only a positive clinical response, and in a 11 patients (9.5%) the response was only polysomnographic. > No response in remaining 25 patients (22%) > Treatment was successful for both clinical and polysomnographic criteria in 57 patients (49%)	Not discussed or mentioned
Moraes-Filho 2014	RCT	> Pantoprazole-Mg 40 mg vs esomeprazole 40 mg 1/day in morning on empty stomach 30 min before breakfast for 4	Not discussed or mentioned	ReQuest-WSO subscale (sleep disturbances component) using patient diary. Sleep disturbances component > Statistically significant reductions from baseline in frequency and intensity of sleep disturbances at weeks 4 and 8 with pantoprazole-Mg

		weeks		and esomeprazole. > The frequency of sleep disturbances as assessed by ReQuest for pantoprazole-Mg significantly decreased from a baseline score of 1.03 to 0.73 at week 4 (p=0.0030) and to 0.49 at week 8 (p=0.0001). - Significant decreases (both p<0.0001) with esomeprazole from baseline (1.28) to week 4 (0.70) and to week 8 (0.68). > The intensity of sleep disturbances as assessed by ReQuest decreased from 1.31 at baseline to 0.86 at week 4 (p=0.0452) and to 0.62 at week 8 (p<0.0001) for pantoprazole-Mg and from a baseline of 1.40 to 0.76 at week 4 (p=0.0162) and to 0.80 at week 8 (p=0.0130) for esomeprazole. > Sleep disturbances continued to improve from week 4 to week 8 for pantoprazole-Mg (frequency: p<0.0001; intensity: p=0.0007), but not for esomeprazole (frequency: p=0.1437; intensity: p=0.5674).
Morales-Arambula 2009	Conference abstract	> Pantoprazole 40 mg 1/day for 4 weeks	Not discussed or mentioned	Frequency of sleep disturbances due to GERD symptoms registered at basal interview by 4 point-Likert scale > Nighttime GERD group had a higher risk of sleep disturbance such as waking up during the night: - Occasionally: OR=4.4 (95%CI: 3.4 to 5.8)

				- Frequent: OR= 8.7 (95%CI: 6.6 to 11.4) - Very frequent: OR= 8.9 (95%CI: 6.4 to 12.3)
Nilsson 2002	RCT	> Laparoscopy > Open surgery	Not discussed or mentioned	PGWB > Preoperatively, 19/25 (76%) in the laparoscopic group reported disturbed sleep due to disease, 19/30 (63%) in the open group and 3/5 (60%) in the converted group > 1 mo after surgery, disturbed sleep decreased to 7/25 (28%) in laparoscopic group, 2/30 (7%) in open group and 1/5 (20%) in converted group; p=0.06 laparoscopy vs open while at 6 mo, 6/25 (24%) in the laparoscopic group, 1/30 (3%) in the open group and 1/5 (20%) in the converted group; p=0.04 laparoscopy vs open
Nilsson 2004	RCT	> Open fundoplication > Laparoscopic fundoplication	Not discussed or mentioned	Structured interviews > The incidence of disturbed sleep decreased after 1 mo and no differences between the laparoscopic and open groups (p=0.061). > At 6 mo, sleep was significantly better in the open group (p=0.043). > After 5 years, there were no differences between the groups (p=656). > Sleep was normalized in majority of patients in both groups.

Orr 2010	Conference abstract	> Baclofen 40 d placebo v given 90 min prior to the start of PSG	PSG > Total sleep time (434 min vs. 379 min, p<0.001), sleep efficiency (91% vs. 79%, p<0.001), and wake after sleep onset (31 min vs. 83 min, p<0.001) with baclofen vs placebo. > Sleep onset latency, percentage of REM sleep and percentage of deep sleep were not different between the groups > REM sleep stages: - Proportion of Stage 1 sleep significantly decreased on baclofen vs placebo (6.8% vs. 10.6%, p<0.05) - No significant differences in the percentage of Stage 2, deep sleep, or REM	Not discussed or mentioned
Orr 2004 [24]	Conference abstract	> Esomeprazole 40 mg vs placebo given 2/day (duration not specified)	PSG > Standard sleep parameters to include sleep efficiency, percent of arousal responses, and sleep onset latency were not different between the placebo and drug conditions.	Not discussed or mentioned
Orr 2007	Cross-over	> Esomeprazole 40 mg vs placebo given 2/day for 1 week, preceding each multichannel intraluminal impedance (MII) and pH	PSG - Total sleep time during placebo and esomeprazole - Sleep efficiency: total sleep time divided by time in bed × 100 during placebo and esomeprazole - Sleep onset latency: minutes from lights out until the participant fell asleep during placebo and	Subjective sleep quality from the 100-point (millimeter) visual analog scale (VAS) obtained from the morning log > No significant difference on the VAS measure of subjective sleep quality whether they were taking placebo or drug

		monitoring sleep laboratory evaluation *Study medications given before breakfast and dinner, preceding each MII and pH monitoring sleep laboratory evaluation.	esomeprazole > no significant differences on various objective sleep measures including total sleep time, sleep efficiency, and sleep onset latency for placebo vs drug conditions.	
Orr 2005	RCT	> Rabeprazole 20 mg vs placebo given 2/day for 1 week	PSG > Mean sleep onset latency was equivalent (18 min). > Objective sleep variables (Placebo [P] vs Drug [D]): - % sleep efficiency (mean ± SEM): P=83.6 ± 2.7; D=86.1 ± 1.8; p-value=NS - % slow wave sleep (stage 3 + stage 4) (mean ± SEM): P=11.6 ± 1.4; D=11 ± 1.4; p-value=NS - % REM sleep (mean ± SEM): P=20.1 ± 1.2; D=18.9 ± 1.6; p-value=NS - Arousals per hour (mean ± SEM): P=14.5 ± 2.3; D=13.6 ± 1.7; p-value=NS	Morning and evening sleep diary and VAS > Mean sleep quality was 5.21 ± 0.37 for placebo and 6.28 ± 0.32 for drug, respectively (z=-2.886, p<0.01). > The mean number of remembered awakenings was significantly reduced with rabeprazole (p<0.001).
Orr 2012	Cross-over	> Baclofen 40 mg vs placebo single dose given 90 min	PSG - Minutes of total sleep time - Sleep onset latency	PSQI, ESS, brief sleep quality questionnaire developed for the study, subjective sleep quality,

		before bed and prior to the combined esophageal pH monitoring/PSG test *treatments randomized in a crossover fashion	- Wake after sleep onset - Sleep efficiency: the minutes of total sleep time divided by minutes in bed × 100 > Objective and subjective measures of sleep were significantly improved by baclofen vs placebo > Total sleep time and sleep efficiency were increased (effect sizes −0.57 and −0.57 respectively) - Total sleep time for placebo: 386.9 (52.9) minutes - Total sleep time for baclofen: 440.8 (18.6) minutes, p<0.001 - Sleep efficiency for placebo: 80.5 (11.0)% - Sleep efficiency for baclofen: 91.7 (3.9)%, p<0.001 > Stage 1 sleep and wake time after sleep onset were decreased (effect sizes −0.54 and −0.57, respectively) - Stage 1 sleep for placebo: 10.1 (6.1)% - Stage 1 sleep for baclofen: 6.1 (3.4)%, p<0.01 - Wake time after sleep onset for placebo: 77.9 (43.3)% - Wake time after sleep onset for baclofen: 27.4 (15.5)%, p<0.001 > Baclofen did not affect sleep onset latency compared with placebo > The % of REM sleep or slow wave sleep was also not altered by baclofen	perceived # of awakenings from sleep, subjective hours of sleep > Subjective # of awakenings and quality of sleep were significantly improved with baclofen vs placebo (effect sizes −0.32 and −0.46, respectively) - Subjective # of awakenings for placebo: 4.8 (4.0) - Subjective # of awakenings for baclofen: 3.1 (2.5), p<0.05 - Subjective sleep quality for placebo: 2.0 (0.7) - Subjective sleep quality for baclofen: 2.9 (0.9) −0.46 p<0.01 > There was a strong trend for subjective hours of sleep to be greater on baclofen vs placebo (effect size: −0.29) - Subjective hours of sleep for placebo: 6.6 (1.8) hours - Subjective hours of sleep for baclofen: 7.4 (0.9) hours, p=0.06

Orr 1998	Cross-over	> Ranitidine 75 mg vs placebo single dose with 10 mL of water at 21:00 hour. * At 22:00 hr, if with heartburn an antacid (Maalox) was given. *treatments randomized in a crossover fashion, with a minimum of 7 days between each of the 2 study nights.	Overnight PSG > No significant differences in PSG measures, nor any differences in the number of Maalox tablets consumed during the night. Sleep parameters in experiment 2, (SEM) > Total sleep time (min), p=0.12 - Ranitidine: 355 (8.9) - Placebo: 330.7 (10.6) > Sleep latency (min), p=0.96 - Ranitidine: 13.7 (4.0) - Placebo: 15.7 (4.4) > WASO (min), p=0.62 - Ranitidine: 39.7 (7.8) - Placebo: 49.5 (9.1) > Sleep efficiency percentage (TST/TIB), p=0.11 - Ranitidine: 85.9 (1.8) - Placebo: 81.3 (1.9) > % REM, p=0.38 - Ranitidine: 18.4 (1.8) - Placebo: 16.1 (1.8) > REM latency (min), p=0.85 - Ranitidine: 121.6 (16.5) - Placebo: 129.5 (16.1) > % SWS, p=0.56 - Ranitidine: 25.1 (1.7) - Placebo: 28.2 (2.5)	> Patient log for arousals from heartburn. > Questionnaire to assess subjective reports of heartburn and sleep disturbance during prior night's study. > significant improvement on all subjective measures of heartburn with ranitidine vs placebo. Awakening by heartburn and questionnaire results (SEM) > # of times awakened by heartburn, p=0.03 - Ranitidine: 0.6 (0.1) - Placebo: 2.0 (0.5) > Sleep interference, p=0.003 - Ranitidine: 0.3 (0.1) - Placebo: 1.4 (0.3) > Severity of the heartburn, p=0.01 - Ranitidine: 1.5 (0.3) - Placebo: 2.9 (0.2) > Effectiveness of drug, p=0.005 - Ranitidine: 0.7 (0.2) - Placebo: 2.4 (0.3)
Orr 2003	RCT	> Ranitidine 150 mg vs placebo together with 10	Overnight PSG > No significant differences between	Morning questionnaire > no significant improvement in

		mL of water, at approximately 21:00 h of the day of pH- or sleep-study Omeprazole 20 mg 2/day for 1 week preceding Ranitidine or Placebo	ranitidine and placebo for any PSG measures > Variables measured (Ranitidine vs. placebo): - Total sleep time, p-val: 0.39 - Sleep onset latency, p-val: 0.14 - Sleep efficiency, p-val: 0.61 - Rapid eye movement sleep, p-val: 0.69 - Slow wave sleep, p-val: 0.9 - Arousal index, p-val: 0.16	subjective measures of heartburn or sleep quality with ranitidine vs placebo > Sleep quality rating - Ranitidine, score (SEM): 2.6 (0.5) - Placebo, score (SEM): 2.2 (0.4) - p-value: not significant"
Orr 2009	Conference abstract	> Baclofen 40 mg vs placebo prior to sleep (duration not specified)	PSG > Total sleep time increased on baclofen (placebo: 385min., baclofen: 438 min, p<0.001). > Total sleep efficiency (placebo: 80%, baclofen: 91%, p<0.001).	Sleep was significantly improved on baclofen in terms of reports of total sleep time, sleep quality and number of awakenings (all p<0.05).
Orr 2009	Other clinical studies (specify)	> Rabeprazole 20 mg given 2/day for 8 weeks	PSG > Sleep-onset latency was significantly (p<0.05) shorter after treatment vs baseline. > Total sleep time (TST and other stages of sleep and arousals were not significantly different after treatment. > no difference in the AHI index at baseline vs after treatment. > TST in min, p=NS - Pre-treatment: 357.0 ± 75.0 minutes - Post-treatment: 374.9 ± 53.2 minutes > SOL in min, p<0.05 - Pre-treatment: 26.2 ± 35.3 minutes	ESS, PSQI > significantly less daytime sleepiness after treatment, which was reflected in a significantly lower ESS score (reported as Figure 1). > The PSQI score was also significantly improved after treatment (reported as Figure 2).

			- Post-treatment: 11.2 ± 9.0 minutes > Sleep efficiency (TST/TIB), p=NS - Pre-treatment: 82.4 ± 13.9 - Post-treatment: 86.3 ± 11.2 > Sleep stage, % of TST - Stage 1, p=NS -- Pre-treatment: 5.14 ± 3.1 -- Post-treatment: 6.5 ± 5.4 - Stage 2, p=NS -- Pre-treatment: 64.1 ± 7.0 -- Post-treatment: 63.3 ± 7.9 - Stage 3/4, p=NS -- Pre-treatment: 9.5 ± 6.5 - Post-treatment: 9.5 ± 6.9 - REM, p=NS -- Pre-treatment 20.3 ± 6.9 -- Post-treatment: 20.1 ± 5.1 > REM-onset latency, min, p=NS - Pre-treatment: 143.0 ± 65.5 minutes - Post-treatment: 129.0 ± 82.3 minutes > Arousals, no., p=NS - Pre-treatment: 46.2 ± 20.0 - Post-treatment: 41.4 ± 19.1	
Oshima 2019	RCT	> Vonoprazan 20 mg vs lansoprazole 30 mg 1/day in morning before breakfast for 14 days.	Not discussed or mentioned	PSQI, Japanese version > Sleep quality significantly improved after 14 days of treatment with vonoprazan, but not with lansoprazole. PSQI scores > Day 0 - Lansoprazole: 8(3-13)

				- Vonoprazan: 6 (2-13) > Day 14, p<0.05 - Lansoprazole: 7.5 (3-15) - Vonoprazan: 5.5 (4-12)*
Pehlivanov 2002	Cross-over	> Cisapride 10 mg vs placebo given 4/day for 5 days then crossover for another 5 days following 2-day washout period	Electroencephalography > mean duration of sleep per patient per night did not differ significantly between the nights on the 2 regimens: 3.7±1.9 h vs. 3.2±2.3 h sleep (p=0.65).	Not discussed or mentioned
Pratha 2003	Conference abstract	> Pantoprazole 40 mg 1/day for 8 days > Ranitidine 150 mg 2/day for 8 days	Not discussed or mentioned	Sleep quality based on daily diaries > Sleep quality based on daily diaries [1 (excellent) to 7 (extremely poor)] - Pantoprazole: 2.76 ± 0.66 for pantoprazole - Ranitidine: 2.94 ± 0.59, p<0.05
Rackoff 2005 [37]	Cohort	> PPI given 2/day concomitantly with either ranitidine 300 mg or famotidine 40 mg	Not discussed or mentioned	Survey (unspecified) conducted through phone interview > The addition of H2RA led to an improvement of GERD-associated sleep disturbance in 18/27 (67%) patients.
Revicki 1998	Open-label or non-RCTs	> Open-label phase: 150 mg of ranitidine 2/day for 6 weeks > Double-blind phase: Either 20 mg omeprazole taken 1/day or	Not discussed or mentioned	HQoL - Sleep scale > Although patients in the omeprazole treatment group had endpoint mean Sleep Scale scores that were 5 points higher than those of the ranitidine group, this difference

		150 mg or ranitidine 2/day. > Treatment was continued for 8 weeks. > Gelusil tablets provided for relief of heartburn, sour stomach, acid indigestion and symptoms of gas as needed, patients were instructed not to consume more than 6 tablets/day.		was not statistically significant (p>0.070).
Revicki 2003	RCT	Clinical Trial 1 - Phase 1 (open label): ranitidine 150 mg 2/day for 6 weeks - Phase 2 (double-blind): omeprazole 20 mg 1/day for 8 weeks ranitidine 150 mg 2/day for 8 weeks > Clinical Trial 2 - omeprazole 20 mg 1/day for 16 weeks	Not discussed or mentioned	MOS sleep disturbance scale > In clinical trial 1, baseline symptom severity was not statistically significantly associated with sleep disturbances scores. > In clinical trial 3, the overall effect of baseline heartburn severity on week 12 sleep disturbance scores was statistically significant (p=0.0471) - The adjusted mean sleep disturbance scores were higher for patients with non/minor heartburn symptoms (mean=75.0, SE=3.8) and moderate heartburn symptoms (mean 71.3, SE=2.9, p=0.0113) compared to those with severe

		- ranitidine 150 mg 2/day for 16 weeks > Clinical Trial 3 - omeprazole 20 mg 1/day for 24 weeks - ranitidine 150 mg 2/day for 24 weeks		symptoms (mean=62.8, SE=2.9, p=0.0315)
Shaheen 2008	Cohort	Rabeprazole 20 mg 2/day for 14 days	Sleep study with measurement of oxygen saturation, PSG, and recording of episodes of awakening > After 2 weeks of treatment, 3 of 4 subjects had normalization of sleep efficiency vs 4 of 12 of the subjects with normal Johnson-DeMeester scores. > no significant differences between the groups for REM sleep %, nor were the pre- and post-therapy values different between refluxers and non-refluxers. > Repeated measures analysis showed significant improvement in spontaneous arousal index between the first (pre-therapy) and second study (post therapy, week 2) for the entire cohort ($p<0.0035$)	FOSQ, ESS > no difference in the FOSQ and ESS scores before and after therapy. Furthermore, the subgroup of subjects with reflux as evidenced by 24-h pH studies demonstrated no significant differences in either their FOSQ or ESS scores before and after therapy, or when compared to the subgroup without reflux.
Smart 1989	RCT	> Trimoprostil 750 mcg vs placebo 4/day for 4 weeks	Not discussed or mentioned	Diary cards > The amount of sleep disturbance declined significantly in both groups

		Aluminum hydroxide tablets allowed ad libitum for symptomatic relief in both groups, no other antacids allowed		(p<0.01, Wilcoxon's signed ranks test; pre- vs post- treatment), but differences between the two groups at the end of the trial did not reach statistical significance.
Suurna 2008	Cross-over	Pantoprazole 40 mg vs placebo 1/day for 2 weeks followed by 2-week washout and crossover	Not discussed or mentioned	ESS, FOSQ > After treatment, a statistically significant improvement was noted in reported symptoms of daytime somnolence (ESS) with pantoprazole when compared with the placebo (p=0.04). > There was a significant sleep-related quality of life (FOSQ) improvement after both pantoprazole and placebo treatment. However, a trend toward greater improvement of FOSQ was noted with pantoprazole (p=0.058).
Symptom relief improves patients' lives: The Canadian feeling thermometer study in patients with uninvestigated reflux disease. 2005	Conference abstract	Esomeprazole 40 mg 1/day for 4 weeks	Not discussed or mentioned	QOLRAD > Before treatment - Substantial impairment in the QOLRAD dimensions: 'eat/drink', 'sleep disturbance', 'vitality' and 'well-being' (mean values 3.8-4.5; best score 7). > After treatment - Patient-rated symptoms improved

				2.9 points (p<0.001). - QOLRAD scores improved 11 points for 'sleep disturbances', 2.0 for 'well-being' and 2.5 for 'eat/drink' (all p<0.001).
Vanderhoof J2003	RCT	> Enfamil AR - formula in amounts adequate for ensuing week, based on 32 oz fed per day - Parents instructed on preparation and use of formula (sole source of nutrition for duration of study) - Volume and frequency of feeding left to parental discretion - Duration of treatment: 5 weeks > Control formula - similar to Enfamil AR except replacement of rice starch with lactose, making the formula	Not discussed or mentioned	Daily diary filled up by parent, trouble sleeping > The most symptomatic infants at baseline had reduction in trouble sleeping significantly with Enfamil AR by the end of the study (p=0.030)

		comparable to standard commercially available cow-milk based infant formulas - Duration of treatment: 5 weeks > Ranitidine anytime after day 7/9 and cisapride any time after day 14/15 - Given as needed after assessment - Dose, frequency and duration of treatment not discussed or mentioned		
Yi 2008	RCT	> Esomeprazole 40mg vs placebo 1/day in morning, 30 min before breakfast, for 8 weeks * Rescue meds: antacids (acid neutralizing capacity, 12mmol H+ per tablet) was	Not discussed or mentioned	PSQI > PSQI decreased significantly after starting treatment with esomeprazole, decreasing from 6.0 at baseline to 3.6 in week 8 ($p<0.01$), but not in the placebo group

		provided with instructions to be taken only as needed for relief of intolerable pain or discomfort throughout the study		

Abbreviations: DST, Digit span test; ESS, Epworth Sleepiness Scale; FOSQ, Functional outcomes sleep questionnaire; FSSG, frequency scale for symptoms of GERD; GSRS, Gastrointestinal Symptoms Rating Scale; MMSE, Mini-Mental Status Exam; MOS, Medical outcomes study; NIH GI PROMIS, National Institute of Health Gastrointestinal Patient-Reported Outcomes Measurement Information System; PGWB, The Psychological General Well-being Index; PSQI, Modified Pittsburg Sleep Quality Index; QOLRAD, Quality of life in reflux and dyspepsia; SHHS, Sleep Heart Health Study Questionnaire; SSI, Insomnia severity index; TMT, Trail making test; WPAI, Work Productivity and Activity Impairment; WPAI-GERD, GERD-specific WPAI

Table S1 References

Aimi M, Komazawa Y, Hamamoto N, et al. Effects of omeprazole on sleep disturbance: Randomized multicenter double-blind placebo-controlled trial. Clinical and Translational Gastroenterology. 2014;5.

Allampati S, Lopez R, Thota PN, Ray M, Birgisson S, Gabbard SL. Use of a positional therapy device significantly improves nocturnal gastroesophageal reflux symptoms. Dis Esophagus. 2017;30(3):1-7.

Aly A, Jamieson GG, Watson DI, Devitt PG, Ackroyd R, Stoddard CJ. An antireflux anastomosis following esophagectomy: a randomized controlled trial. Journal of Gastrointestinal Surgery. 2010;14(3):470-5.

Cadiot G, Delaage P, Fabry C, Barthelemy P. Sleep disturbance associated with gastro-oesophageal reflux disease (GORD): Frequency and evolution with treatment according to patients. Gastroenterology. 2008;134(4):A169.

Chand N, Johnson DA, Tabangin M, Ware JC. Sleep dysfunction in patients with gastro-oesophageal reflux disease: prevalence and response to GERD therapy, a pilot study. Aliment Pharmacol Ther. 2004;20(9):969-74.

Chen C, Kuo TB. The effect of acid suppression on subjective sleep, gastric myoelectrical functioning, and cardiac autonomic function in patients with erosive GERD. Gastroenterology. 2006;130(4):A175.

Chey WD, Mody R, Chen L, et al. Nighttime symptoms and sleep impairment among patients with gastro-esophageal reflux disease (GERD) receiving prescription (rx) proton pump inhibitors (PPIs). Gastroenterology. 2008;134(4):A324.

Cihang G, Olszewski T, King KL, Vaezi MF, Niswender KD, Silver HJ. The effects of modifying amount and type of dietary carbohydrate on esophageal acid exposure time and esophageal reflux symptoms: A randomized controlled trial. Am J Gastroenterol. 2022;117(10):1655-1667.

Clayton SB, Rife C, Singh E, Castell DO. Proton pump inhibitors do not decrease the frequency of reflux episodes during nocturnal recumbency. Gastroenterology. 2011;140(5):S581.

DeVault KR, Holtmann G, Malagelada JR, Schmitt H, Chassany O. Pantoprazole 40 mg (PANTO) is superior to esomeprazole 40 mg (ESO) in resolving sleep disturbances in GERD patients. Am J Gastroenterol. 2006;101(9):S400.

Dewan R, Nischal N, Nehru R, Negi M, Goyal P. Effect of nocturnal awakening due to gastroesophageal reflux disease on neurocognitive functions and response to proton pump inhibitors. Indian Journal of Gastroenterology. 2011;30(1):A20.

DiManno AJ,Jr, Banwait KS, Eschinger E, Greenberg A, Doghramji K, Cohen S. Sleep efficiency; effect of PPI therapy in patients with marked sleep disturbance. Gastroenterology. 2004;126(4):A341.

Donnelly MG, Alexander I, Clarkson J, et al. Single-dose non-prescription ranitidine 75mg is superior to single-dose omeprazole 20mg for prevention of postprandial and nighttime heartburn following a provocative meal. Am J Gastroenterol. 2003;98(9):S4.

Fass R, Skszek S, Green C, et al. Effect of anti-reflux treatment on sleep of patients with gastroesophageal reflux disease (GERD) - a randomized, double blind, placebo-controlled trial. Gastroenterology. 2004;126(4):A57.

Fass R, Johnson DA, Orr WC, Han C, Mody R, Stern KN, Pilmer BL, Perez MC. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. Am J Gastroenterol. 2011;106(3):421-31.

Fujiwara Y, Habu Y, Ashida K, Kusano M, Higuchi K, Arakawa T. Sleep disturbances and refractory gastroesophageal reflux disease symptoms in patients receiving once-daily proton pump inhibitors and efficacy of twice-daily rabeprazole treatment. Digestion. 2013;88(3):145-152.

Fujiwara Y, Kohata Y, Kaji M, et al. Sleep dysfunction in Japanese patients with gastroesophageal reflux disease: prevalence, risk factors, and efficacy of rabeprazole. Digestion. 2010;81(3):135-141.

Gagliardi GS, Shah AP, Goldstein M, et al. Effect of zolpidem on the sleep arousal response to nocturnal esophageal acid exposure. Clin Gastroenterol Hepatol. 2009;7(9):948-952.

Gerson LB, Fass R. A systematic review of the definitions, prevalence, and response to treatment of nocturnal gastroesophageal reflux disease. Clinical Gastroenterology and Hepatology. 2009;7(4):372-378.

Giannini EG, Zentilin P, Dulbecco P, Vigneri S, Scarlata P, Savarino V. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment. Am J Gastroenterol. 2008;103(2):267-275.

Guda N, Partington S, Shaw MJ, Leo G, Vakil N. Unrecognized GERD symptoms are associated with excessive daytime sleepiness in patients undergoing sleep studies. Dig Dis Sci. 2007;52(10):2873-2876.

Gunasekaran T, Tolia V, Colletti RB, et al. Effects of esomeprazole treatment for gastroesophageal reflux disease on quality of life in 12- to 17-year-old adolescents: an international health outcomes study. BMC Gastroenterol. 2009;9:84.

Hansen ÅN, Bergheim R, Fagertun H, Lund H, Wiklund I, Moum B. Long-term management of patients with symptoms of gastro-oesophageal reflux disease - A Norwegian randomised prospective study comparing the effects of esomeprazole and ranitidine treatment strategies on health-related quality of life in a general practitioners setting. Int J Clin Pract. 2006;60(1):15-22.

Hawkey CJ, Talley NJ, Scheiman JM, et al. Maintenance treatment with esomeprazole following initial relief of non-steroidal anti-inflammatory drug-associated upper gastrointestinal symptoms: the NASA2 and SPACE2 studies. Arthritis Res Ther. 2007;9(1):R17.

Hawkey CJ, Yeomans ND, Jones R, et al. Esomeprazole improves quality of life in patients with upper GI symptoms associated with long-term NSAID therapy. Digestive Dis Week. 2003:102214.

Hayashi Y, Fujiwara Y, Arakawa T. Prospective multicenter study of sleep disturbance in patients who are refractory to daily proton pump inhibitor therapy and efficacy of twice-daily rabeprazole. Gastroenterology. 2013;144(5):S206.

Hiramoto K, Fujiwara Y, Ochi M, et al. Effects of esomeprazole on sleep in patients with gastroesophageal reflux disease as assessed on actigraphy. Intern Med. 2015;54(6):559-565.

Hunt RH, Armstrong D, Moayyedi P, Lei Y, Bukoski M, White RJ. Improvement in sleep disturbance in patients with persistent GERD symptoms after a change in therapy: EncomPASS - a cluster-randomized study in primary care. Gastroenterology. 2009;136(5):A440.

Ing AJ, Ngu MC, Breslin AB. Obstructive sleep apnea and gastroesophageal reflux. Am J Med. 2000;108 Suppl 4a:120S-125S.

Jha LK, Fass R, Gadam R, et al. The Effect of Ramelteon on Heartburn Symptoms of Patients With Gastroesophageal Reflux Disease and Chronic Insomnia: A Pilot Study. J Clin Gastroenterol. 2016;50(2):e19-e24.

Jha LK, Hershcovici T, Gadam R, Fass OZ, Webster MR, Fass R. The effect of anti-reflux treatment on acid reflux and conscious awakenings from sleep in patients with gastroesophageal reflux disease. Gastroenterology. 2012;142(5):S592.

Jha LK, Maradey-Romero C, Gadam R, et al. The effect of antireflux treatment on the frequency of awakenings from sleep in patients with gastroesophageal reflux disease. Neurogastroenterology and Motility. 2015;27(2):237-245.

Johannessen R, Petersen H, Olberg P, Johnsen G, Fjøsne U, Kleveland PM. Airway symptoms and sleeping difficulties in operated and non-operated patients with gastroesophageal reflux disease. Scand J Gastroenterol. 2012;47(7):762-769.

Johnson D, Crawley JA, Hwang C, Brown K. Clinical trial: esomeprazole for moderate-to-severe nighttime heartburn and gastro-oesophageal reflux disease-related sleep disturbances. Aliment Pharmacol Ther. 2010;32(2):182-190.

Johnson D, Holmes L, May J, Ware JC. GERD induced sleep disorders and a reversible driving impairment with esomeprazole - A prospective pilot study. Am J Gastroenterol. 2010;105:S13.

Johnson DA, Crawley JA, Hwang C, Brown KA. Effect of esomeprazole on sleep quality in patients with gastroesophageal reflux disease (GERD)-related sleep disturbances. Gastroenterology. 2009;136(5):A71.

Johnson DA, Crawley JA, Hwang C, Brown KA. Effect of esomeprazole on work productivity and regular daily activities in patients with gastroesophageal reflux disease (GERD)-related sleep disturbances. Gastroenterology. 2009;136(5):A492.

Johnson DA, Hwang C, Brown KA. Esomeprazole for the relief of nighttime heartburn in patients with gastroesophageal reflux disease (GERD)-related sleep disturbances. Gastroenterology. 2009;136(5):A435.

Johnson DA, Le Moigne A, Hugo V, Nagy P. Rapid resolution of sleep disturbances related to frequent reflux: effect of esomeprazole 20 mg in two randomized, double-blind, controlled trials. Curr Med Res Opin. 2015;31(2):243-50.

Johnson DA, Lemoigne A, Hugo V, Nagy P. Relief and resolution of GERD-related sleep disturbances with esomeprazole 20 mg: Results from two randomized, double-blind trials in subjects with frequent nighttime heartburn and associated sleep disturbance. Gastroenterology. 2014;146(5):S760-S761.

Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: A randomized, placebo-controlled trial. Am J Gastroenterol. 2005;100(9):1914-1922.

Katz P, DeVault K, Edmundowicz S, Schlack-Haerer S, Ganz R. Improvement in symptoms and QOL is sustained with minimal side effects 4 years after magnetic sphincter augmentation (LINX) for GERD. Am J Gastroenterol. 2014;109:S34.

Kawai T, Hirayama Y, Oguchi A, et al. Effects of rikkunshito on quality of life in patients with gastroesophageal reflux disease refractory to proton pump inhibitor therapy. Journal of Clinical Biochemistry and Nutrition. 2017;60(2):143-145.

Kawami N, Hoshino S, Hoshikawa Y, et al. Efficacy of rikkunshito for functional heartburn: A prospective pilot study. Journal of Nippon Medical School. 2022;89(1):56-65.

Khan BA, Sodhi JS, Zargar SA, et al. Effect of bed head elevation during sleep in symptomatic patients of nocturnal gastroesophageal reflux. J Gastroenterol Hepatol. 2012;27(6):1078-1082.

Kim JS, Seo SI, Kang SH, et al. Effects of Tegoprazan Versus Esomeprazole on Nighttime Heartburn and Sleep Quality in Gastroesophageal Reflux Disease: A Multicenter Double-blind Randomized Controlled Trial. J Neurogastroenterol Motil. 2023;29(1):58-64.

Kindt S, Imschoot J, Tack J. Prevalence of and impact of pantoprazole on nocturnal heartburn and associated sleep complaints in patients with erosive esophagitis. Diseases of the Esophagus. 2011;24(8):531-537.

Kulig M, Leodolter A, Vieth M, et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease - an analysis based on the ProGERD initiative. Alimentary Pharmacology and Therapeutics. 2003;18(8):767-776.

Laine L, Dhir V. Helicobacter pylori eradication does not worsen quality of life related to reflex symptoms: A prospective trial. Aliment Pharmacol Ther. 2002;16(6):1143-48.

Lauritsen K, Junghard O, Eklund S, Wiklund I. The effect of esomeprazole 40 mg on healing, reflux symptoms and quality of life in patients with reflux oesophagitis. Gut. 2002;51:A167.

Leodolter A, Kulig M, Nocon M, et al. Esomeprazole therapy improves sleep disorders in patients with gastroesophageal reflux disease (GERD): A report from the ProGerd study. Digestive Dis Week. 2003:104621.

López-Alvarenga JC, Orr W, Vargas-Romero J, et al. Relief of night-time symptoms associated with gastroesophageal reflux disease following 4 weeks of treatment with pantoprazole magnesium: The Mexican gastroesophageal reflux disease working group. Journal of Neurogastroenterology and Motility. 2014;20(1):64-73.

Maiti R, Jaida J, John Israel PL, Koyagura N, Mukkisa S, Palani A. Rabeprazole and esomeprazole in mild-to-moderate erosive gastroesophageal reflux disease: A comparative study of efficacy and safety. Journal of Pharmacology and Pharmacotherapeutics. 2011;2(3):150-157.

Mann SG, Murakami A, McCarroll K, Rao AN, Cottrell J, Mehentee J, Morton R. Low dose famotidine in the prevention of sleep disturbance caused by heartburn after an evening meal. Alimentary pharmacology & therapeutics. 1995;9(4):395-401.

Masihi M, Doerfler B, Kia L, et al. Nutrition interventions improve gastroesophageal reflux symptoms among GERD patients who successfully stopped taking proton pump inhibitors (PPI). preliminary results of the NU-GERD diet study. Am J Gastroenterol. 2020;115:S182-S183.

Mathias SD, Colwell HH, Miller DP, Pasta DJ, Henning JM, Ofman JJ. Health-related quality-of-life and quality-days incrementally gained in symptomatic nonerosive GERD patients treated with lansoprazole or ranitidine. Digestive diseases and sciences. 2001;46(11):2416-23.

Moayyedi P, Hunt R, Armstrong D, Lei Y, Bukoski M, White R. The impact of intensifying acid suppression on sleep disturbance related to gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther. 2013;37(7):730-737.

Modolell I, Esteller E, Segarra F, Mearin F. Proton-pump inhibitors in sleep-related breathing disorders: clinical response and predictive factors. Eur J Gastroenterol Hepatol. 2011;23(10):852-858.

Moraes-Filho J, Pedroso M, Quigley EMM. Randomised clinical trial: Daily pantoprazole magnesium 40 mg vs. esomeprazole 40 mg for gastro-oesophageal reflux disease, assessed by endoscopy and symptoms. Alimentary Pharmacology and Therapeutics. 2014;39(1):47-56.

Morales-Arambula M, Sobrino-Cossio S, Vargas J, et al. Nighttime GERD: Prevalence, symptom intensity and treatment response to a 4 week treatment with 40 mg of pantoprazole magnesium OD a report from the GERD mexican working group. Gastroenterology. 2009;136(5):A428.

Nilsson G, Larsson S, Johnsson F. Randomized clinical trial of laparoscopic versus open fundoplication: evaluation of psychological well-being and changes in everyday life from a patient perspective. Scandinavian journal of gastroenterology. 2002;37(4):385-91.

Nilsson G, Wenner J, Larsson S, Johnsson F. Randomized clinical trial of laparoscopic versus open fundoplication for gastro-oesophageal reflux. Br J Surg. 2004;91(5):552-559.

Orr W, Goodrich S, Shepherd K, Wright S, Mellow M. Baclofen decreases reflux and improves sleep quality in individuals with nighttime heartburn. Am J Gastroenterol. 2010;105:S22.

Orr W, Hunter MD, Goodrich S. Sleep patterns and arousal responses under conditions of powerful acid suppression. Gastroenterology. 2004;126(4):A57.

Orr WC, Craddock A, Goodrich S. Acidic and non-acidic reflux during sleep under conditions of powerful acid suppression. Chest. 2007;131(2):460-5.

Orr WC, Goodrich S, Robert J. The effect of acid suppression on sleep patterns and sleep-related gastro-oesophageal reflux. Aliment Pharmacol Ther. 2005;21(2):103-8.

Orr WC, Goodrich S, Wright S, Shepherd K, Mellow M. The effect of baclofen on nocturnal gastroesophageal reflux and measures of sleep quality: a randomized, cross-over trial. Neurogastroenterol Motil. 2012;24(6):553-9, e253.

Orr WC, Harnish MJ. Sleep-related gastro-oesophageal reflux: provocation with a late evening meal and treatment with acid suppression. Aliment Pharmacol Ther. 1998;12(10):1033-8.

Orr WC, Harnish MJ. The efficacy of omeprazole twice daily with supplemental H2 blockade at bedtime in the suppression of nocturnal oesophageal and gastric acidity. Alimentary pharmacology & therapeutics. 2003;17(12):1553-8.

Orr WC, Mellow M, Vu U, Goodrich S. The effect of baclofen on sleep measures and sleep related gastroesophageal reflux (GER). Gastroenterology. 2009;136(5):A434.

Orr WC, Robert JJ, Houck JR, Giddens CL, Tawk MM. The effect of acid suppression on upper airway anatomy and obstruction in patients with sleep apnea and gastroesophageal reflux disease. J Clin Sleep Med. 2009;5(4):330-334.

Oshima T, Arai E, Taki M, et al. Randomised clinical trial: vonoprazan versus lansoprazole for the initial relief of heartburn in patients with erosive oesophagitis. Aliment Pharmacol Ther. 2019;49(2):140-146.

Pehlivanov N, Sarosiek I, Whitman R, Olyaee M, McCallum R. Effect of cisapride on nocturnal transient lower oesophageal sphincter relaxations and nocturnal gastro-oesophageal reflux in patients with oesophagitis: a double-blind, placebo-controlled study. Alimentary pharmacology & therapeutics. 2002;16(4):743-7.

Pratha V, Wan GJ, Soffer E, Hogan D, Wang W. Pantoprazole positively impacts nighttime heartburn symptoms and quality of sleep in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2003;98(9):S234-S235.

Rackoff A, Agrawal A, Hila A, Mainie I, Tutuian R, Castell DO. Histamine-2 receptor antagonists at night improve gastroesophageal reflux disease symptoms for patients on proton pump inhibitor therapy. Diseases of the Esophagus. 2005;18(6):370-373.

Revicki DA, Sorensen S, Maton PN, Orlando RC. Health-related quality of life outcomes of omeprazole versus ranitidine in poorly responsive symptomatic gastroesophageal reflux disease. Dig Dis. 1998;16(5):284-291.

Revicki DA, Zodet MW, Joshua-Gotlib S, Levine D, Crawley JA. Health-related quality of life improves with treatment-related GERD symptom resolution after adjusting for baseline severity. Health and Quality of Life Outcomes. 2003;1.

Shaheen NJ, Madanick RD, Alattar M, et al. Gastroesophageal reflux disease as an etiology of sleep disturbance in subjects with insomnia and minimal reflux symptoms: a pilot study of prevalence and response to therapy. Dig Dis Sci. 2008;53(6):1493-1499.

Smart HL, James PD, Atkinson M, Hawkey CJ. Treatment of reflux oesophagitis with trimoprostil. Digestion. 1989;44(1):52-6.

Suurna MV, Welge J, Surdulescu V, Kushner J, Steward DL. Randomized placebo-controlled trial of pantoprazole for daytime sleepiness in GERD and obstructive sleep disordered breathing. Otolaryngology—Head and Neck Surgery. 2008;139(2):286-90.

Symptom relief improves patients lives: The Canadian feeling thermometer study in patients with uninvestigated reflux disease. Gastroenterology. 2005;128(4):A289.

Vanderhoof JA, Moran JR, Harris CL, Merkel KL, Orenstein SR. Efficacy of a Pre-thickened Infant Formula: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Parallel Group Trial in 104 Infants with Symptomatic Gastroesophageal Reflux. Clinical pediatrics. 2003;42(6):483-95.

Yi CH, Chen CL, Kuo TB, Yang CC. The effect of acid suppression on sleep and cardiac autonomic regulation in GERD. Hepatogastroenterology. 2008;55(86-87):1649-1652.

Table S2. Synopsis of Study 1

PROTOCOL TITLE: A Randomized, Single-Dose Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When
Administered 10 Minutes Prior to a Provocative Meal
PRIMARY THERAPY PERIOD: 14-Jan-1998 to 17-Mar-1998. Study is complete.
CLINICAL PHASE: III
DURATION OF TREATMENT: The study included a 3-hour screening meal session and 3-hour treatment meal session followed by at-home evaluation period until 8 AM the following morning. The study lasted 8 weeks.

DIAGNOSIS/INCLUSION CRITERIA: Male or female patients at least 18 years of age with a history of food-induced heartburn of at least 2 months' duration with at least 3 episodes per week of moderate to severe intensity, and who use antacids or OTC acid reducers.
EVALUATION CRITERIA: Efficacy: heartburn severity evaluations (0=none, 1=mild, 2=moderate, 3=severe) at 30-minute intervals for the 3-hour period after both the screening and treatment meals, and a global evaluation of efficacy (0=poor, 1=fair, 2=good, 3=very good, 4=excellent) on the morning after treatment. Awakenings with heartburn and rescue medication use were also collected. Safety: adverse experiences were reported during the screening and treatment meal sessions through 8 AM the following morning.
STATISTICAL PLANNING AND ANALYSIS: (1) Peak heartburn severity during the 3 hours following the start of the provocative meal [primary parameter] and (2) global assessment of efficacy measured at the end of the treatment period were analyzed using logistic regression models for ordered categorical data. (3) The proportion of patients who reported no heartburn symptoms during the 3 hours following the start of the meal and (4) the proportion of patients who did not awaken with heartburn were analyzed using logistic regression models for binary data. (5) Mean heartburn severity during the 3 hours following the start of the meal was analyzed using an ANOVA model. All models included factors for treatment group and investigator site. Because only one treatment comparison was performed for the primary hypothesis (famotidine 20 mg versus famotidine 10 mg for peak heartburn severity), no correction for multiple comparisons was made. Sample size: n=260 patients per treatment group had from 73 to 99% power to detect an 11- to 20-percentage-point difference between famotidine 20 mg and famotidine 10 mg for percentage of patients with none or mild peak heartburn during the 3 hours following the start of the provocative meal (a=0.050, two-tailed).

RESULTS: Summaries of the Efficacy and Safety Results are shown in the following tables.
Efficacy: (All-Patients-Treated)

	Famotidine 20 mg (n=261)	Famotidine 10 mg (n=271)	Placebo (n=262)
PRIMARY: % none or mild peak heartburn severity during 3 hours postmeal	36%**f	29%	22%
% reporting no heartburn during 3 hours postmeal	11%**	8%+	4%
Mean heartburn severity during 3 hours postmeal	1.20**	1.32*	1.46
% good/very good/excellent global assessent †	56%**f	47%*	39%
% Reporting no awakenings with heartburn	60%**	57%**	43%

† Statistical significance based on analysis of all categories of peak heartburn severity and global assessment.
+ 0.05 < p£0.10 vs. placebo; * p£0.05 vs. placebo; ** p£0.01 vs. placebo; f 0.05 < p£0.10 vs. famotidine 10 mg
Note: Famotidine 20 mg versus famotidine 10 mg = primary treatment comparison for peak heartburn severity. Not all patients had data available for all efficacy parameters.

Safety: (All-Patients-Treated)

	Adverse Experience Summary—Double-Blind Phase		
Clinical adverse experiences (AEs) Number (%) of patients:	Famotidine 20 mg (n=261) n (%)	Famotidine 10 mg (n=271) n (%)	Placebo (n=262) n (%)
With one or more AEs	9 (3.4)	10 (3.7)	10 (3.8)
With no AEs	252 (96.6)	261 (96.3)	252 (96.2)

With drug-related AEs	1 (0.4)	2 (0.7)	2 (0.8)
With serious AEs	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to an AE	0 (0.0)	0 (0.0)	0 (0.0)

Table S3. Synopsis of Study 2

PROTOCOL TITLE: A Randomized, Single-Dose, Double-Blind, Parallel Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing
Heartburn Symptoms When Administered 10 Minutes Prior to a Provocative Meal
CLINICAL PHASE: III
DURATION OF TREATMENT: Qualified patients received a dose of study medication 10 minutes prior to a provocative meal. Heartburn severity was evaluated for 3 hours following the meal.
DIAGNOSIS/INCLUSION CRITERIA: Male and female patients at least 18 years of age with a history of food-induced heartburn of at least 2 months' duration with at least 3 episodes per week. Patients must have experienced heartburn which was frequently severe, (30% of their episodes; heartburn severity was determined by self-evaluation). Patients must have been able to identify specific foods and beverages that produced their symptoms.
EVALUATION CRITERIA: Efficacy: heartburn severity evaluations at 30-minute intervals (1=mild, 2=moderate, 3=severe) for the 3-hour period following the treatment meal. Heartburn symptoms experienced during the overnight evaluation period; and global evaluation of efficacy at end of the overnight evaluation period (0=poor, 1=fair, 2=good, 3=very good, 4=excellent). Safety: Adverse experiences were monitored throughout this study; nonserious adverse experiences were recorded during the baseline run-in and treatment session through 8 AM the following morning.
STATISTICAL PLANNING AND ANALYSIS: (1) Peak heartburn severity during the 3 hours following the start of the provocative meal (primary parameter) and (2) global assessment of efficacy measured at the end of the treatment period were analyzed using logistic regression models for ordered categorical data. (3) The proportion of patients who reported no heartburn symptoms during the 3 hours following the start of the meal, (4) the proportion of patients who did not awaken with heartburn, and (5) the proportion of patients who used rescue medication during the study were analyzed using logistic regression models for binary data. (6) Mean heartburn severity during the 3 hours following the start of the meal was analyzed using an ANOVA model. All models included factors for treatment group and investigator site. Because only one treatment comparison was performed for the primary hypothesis (famotidine 20 mg versus famotidine 10 mg for peak heartburn severity), no correction for multiple comparisons was made. Sample size: n=500 patients per active treatment group and 250 patients in the placebo group had from 60 to 89% power to detect a 7- to 10-percentage-point difference between famotidine 20 mg and famotidine 10 mg, and from 73 to 95% power to detect a 10- to 14-percentage point difference between active treatment group and placebo, for percentage of patients with none or mild peak heartburn during the 3 hours following the start of the provocative meal (a=0.050, two tailed).
RESULTS: Summaries of the Efficacy and Safety Results are shown in the following tables.
Efficacy: (All-Patients-Treated)

	Famotidine 20 mg (n=488)	Famotidine 10 mg (n=490)	Placebo (n=249)
PRIMARY: % none or mild peak heartburn severity during 3 hours postmeal†	70%**FF	61%**	50%
% reporting no heartburn during 3 hours postmeal	38%**FF	30%**	19%
Mean heartburn severity during 3 hours postmeal	0.53**FF	0.65**	0.78
% good/very good/excellent global assessent †	69%**F	65%**	48%
% Reporting no awakenings with heartburn	70%**	69%**	53%
% Using rescue medication during the study	23%**	25%**	37%

† Statistical significance based on analysis of all categories of peak heartburn severity and global assessment.
** p £0.01 versus placebo; F p £0.05 versus famotidine 10 mg; FF p £0.01 versus famotidine 10 mg
Note: Famotidine 20 mg versus famotidine 10 mg = primary treatment comparison for peak heartburn severity.
Not all patients had data available for all efficacy parameters.

Safety: (All-Patients-Treated)

	Adverse Experience Summary—Double-Blind Phase		
Clinical adverse experiences (AEs)	Famotidine 20 mg (n=489) n (%)	Famotidine 10 mg (n=491) n (%)	Placebo (n=249) n (%)

Number (%) of patients:			
With one or more AEs	12 (2.5)	16 (3.3)	11 (4.4)
With no AEs	477 (97.5)	475 (96.7)	238 (95.6)
With drug-related AEs	3 (0.6)	6 (1.2)	5 (2.0)
With serious AEs	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to an AE	0 (0.0)	0 (0.0)	0 (0.0)

Table S4. Synopsis of Study 3

PROTOCOL TITLE: A Double-Blind, Parallel Study to Evaluate the Efficacy and Tolerability of Famotidine 10 mg vs. Placebo in Prevention of Postprandial Heartburn Symptoms and Interference With Sleep Induced by an Evening Test Meal
CLINICAL PHASE: IV
DURATION OF TREATMENT: The study consisted of 3 study visits with the treatment phase (administration of drug and provocative meal) occurring between Visits 2 and 3. Visits 1 (screening) and 2 (randomization) were separated by up to 15 days. The treatment phase of the study occurred within 2 days of Visit 2 and lasted from 7 PM of the evening study medication was taken until the morning of the next day. One dose of study medication was planned. Visit 3 (follow-up) took place within 2 days of the start of the treatment phase. The occurrence of adverse events was monitored from the time of administration of study drug until noon of the following day.
DIAGNOSIS/INCLUSION CRITERIA: Male and female patients at least 21 years of age with a history of heartburn of at least 2 months duration, with at least 3 episodes per week. Patients must have regularly experienced interference with sleep due to heartburn and must have been able to identify specific foods and beverages that produce heartburn symptoms. Patients also must have regularly used antacids for effective relief of their discomfort.
EVALUATION CRITERIA: Efficacy: Primary - Patients completed a five-point global assessment of how well the study drug controlled heartburn symptoms during the night. Secondary - Patients completed five-point global assessments of interference with falling asleep due to heartburn and control of meal-induced heartburn during the 3 hours following the meal. Patients also assessed the severity of their heartburn symptoms on a six-point scale immediately before consuming the meal, 30 minutes after the meal began, and thereafter at 15-minute intervals for a total of 3 hours. Safety: Adverse experiences were evaluated for maximum intensity, seriousness, and drug relationship.
STATISTICAL PLANNING AND ANALYSIS: Efficacy: The primary approach to the analysis was an all-patients-treated approach. The primary parameter, global assessment of control of meal-induced heartburn during the night, was analyzed by fitting a model to the mean scores using the weighted least squares method as implemented by PROC CATMOD in SAS. Secondary parameters were also analyzed using this method. Chi-square tests were used when this method was not appropriate. With 130 patients per treatment group, the study had 96% power to detect a 0.8 reduction in mean scores for famotidine compared to placebo, assuming an alpha level of 0.05 and a two-tailed test. Safety: Treatment groups were compared with respect to the incidence of adverse experiences using Fisher's exact test.
RESULTS: Efficacy - The following results are from the all-patients-treated population of 304 patients (156 on famotidine and 148 on placebo). Ninety-five patients (60.9%) rated famotidine as excellent in the assessment of control of meal-induced heartburn during the night compared to 62 patients (41.9%) in the placebo group. The difference between the treatment groups with respect to mean scores was statistically significant, indicating significantly better assessments in the famotidine group than in the placebo group. Similar results were seen for the following secondary efficacy variables: global assessment of interference with falling asleep, peak heartburn severity, and global assessment of control of meal-induced heartburn during the 3-hour postmeal period. One hundred thirty-seven patients (87.8%) on famotidine did not require rescue medication compared to 103 patients (69.6%) on placebo. Seventy-seven patients (49.4%) on famotidine did not experience any heartburn during the study compared to 48 patients (32.4%) on placebo. The difference between treatment groups was statistically significant.

Safety - Of the 305 patients evaluated for safety (156 on famotidine and 149 on placebo), thirteen patients (8.3%) on famotidine reported one or more clinical adverse experiences compared to 17 patients (11.4%) on placebo. This difference was not statistically significant. Although three patients on famotidine (FAM) 10 mg were hospitalized, none were related to the study medication and all recovered, as summarized in the following table:

Listing of Patients With Serious Clinical Adverse Experiences

AN	Gender/ Age	Site	Treatment Group	Adverse Experience	Onset Date Relative to Visit 2	Duration	Intensity	Action Taken	Recovered	Drug Relation-ship
0124	M/39	011	FAM 10 mg	Palpitations	7	4 hours	Severe	None	Yes	Def. Not
0302	M/46	008	FAM 10 mg	Infection, skin	2	4 days	Severe	None	Yes	Def. Not
0412	F/76	028	FAM 10 mg	Chest pain	2	20 min	Moderate	None	Yes	Def. Not