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BACLOFEN'S OUTCOME ON GASTROESOPHAGEAL REFLUX DISEASE TREATMENT: A ARBITRARY CONTROLLED EXPERIMENTS BY META-ANALYSIS

Md. Harun-Or-Rashid, Sharif M. Shaheen, Md. Mizanur Rahman, A. K. Azad, Md. Mamunur Rashid Munna and Most. Nazmin Akter

Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Daffodil Tower (DT)-054/2 Sobahanbag, Mirpur Road, Dhanmondi, Dhaka-1207, Bangladesh.

Email address: harun.1947.1952@gmail.com

Abstract

Objectives: By increasing the occurrence of transient lower esophageal sphincter relaxation, baclofen can alleviate gastroesophageal reflux-related symptoms in healthy subjects and patients with gastroesophageal reflux disease (GERD).

Methods: We systematically searched PubMed, Medline, Embase, ScienceDirect, ClinicalTrials.gov and the Cochrane Central Database of Randomized Controlled Trials for randomized controlled trials conducted prior to November 2019. We also carried out a meta-analysis of all qualifying trials.

Results: A total 283 patients and healthy subjects were identified in nine studies. Comparative analysis provided high-quality data supporting baclofen's ability to promote a short-term reduction in the number of reflux episodes per patient, the average length of reflux episodes, and the frequency of intermittent lower relaxation of the esophageal sphincter. There had been no documented serious adverse effects or death events, and there were no significant differences between baclofen and placebo in the total adverse events. All reported baclofen side effects were mild to moderate, and the medication was well tolerated.

Inference: Substantial evidence suggests that baclofen may be a successful approach to treating GERD patients; however, this recommendation would be further supported by a larger well-designed trial.

Keywords: *Gastroesophageal reflux disease (GERD), Baclofen, Esophageal sphincter, Meta-analysis.*

Introduction

Gastroesophageal reflux ailment (GERD), which is defined as a disease resulting from the reflux of gastric contents into the esophagus, has lengthy been a distinguished difficulty worldwide. Gastric reflux can evoke tense signs, which include heartburn and regurgitation, and further complications, together with erosive esophagitis, also can occur [1–3]. The ailment may be labeled into 3 subtypes: nonerosive reflux ailment, hypersensitive esophagus, and purposeful heartburn [4]. Endoscopic or microscopic proof of damage to the esophageal mucosa may be found for GERD patients, although the body undergoes initial attempts to guard itself through tightening the gastroesophageal junction, a muscular complex together with the decrease esophageal sphincter, the agricultural diaphragm, and the gastric sling [5, 6]. Recent proof shows that transient lower esophageal sphincter relaxation (TLESR) might be the primary reason of reflux episodes in sufferers with GERD [7, 8].

Proton pump inhibitors [9] and histamine type 2 receptor antagonists [10] are first-line remedy for patients with GERD. Both methods depend commonly on the inhibition of acid secretion. Despite their excessive performance in symptom decision and esophageal mucosal restoration, medical failure has grow to be a commonplace predicament for sufferers with GERD [11]. The number one motive for the scientific failure may be the lack of ability of these sellers to govern TLESR.

As an trade technique to the treatment of GERD, baclofen, a GABAB agonist, reduces the frequency of reflux activities and inhibits TLESR [8]. Numerous randomized managed trials (RCTs) over the last decade have pointed to the healing efficacy of baclofen for GERD. However, maximum of those research are of restricted size, and, consequently, the position of baclofen within the remedy of GERD remains unsupported. In this take a look at, a meta-evaluation of applicable RCTs [12–20] changed into achieved to assist the clinical efficacy and protection of baclofen for the treatment of GERD.

Methods

Data Sources

We finished an independent evaluation of Medline, PubMed, ScienceDirect, and Embase databases to pick out RCTs from January 1978 to November 2013 the use of "baclofen" and "GERD" as seek key words. The seek became constrained to human research and RCTs posted in English. We also manually searched abstracts and complete-text articles containing the identical seek terms from ClinicalTrials.Gov and the Cochrane Central Register of Controlled Trials to perceive doubtlessly relevant RCTs that have been published before November 2013. An unbiased search of Google Scholar become also carried out to make certain that no scientific trials had been neglected. To find extra articles relevant to the content material of our meta-analysis, references from probably applicable articles have been additionally personally researched [21, 22]. Studies had been decided on and systemically reviewed in line with the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23].

Study Selection/Inclusion Criteria

We decided on studies for this meta-analysis according to the following criteria: (1) research had been randomized double-blind trials that examine baclofen and placebo for GERD; (2) research determined the efficacy and safety of baclofen for the remedy of GERD; (3) studies stated unique records regarding symptomatic remedy and destructive activities. Abstracts of medical conferences have been excluded within the meta-evaluation, as well as trials that focused on pharmacokinetic or pharmacodynamic variables. We included both unmarried dose and a couple of dose/crossover research. We additionally covered studies in which baclofen was given either on my own or as an addition to proton pump inhibitors.

Data Extraction

Two investigators (SJ. Li and SY. Shi) independently screened statistics from trials according to the inclusion standards. We extracted statistics from the studies, which includes the type of observe, the sufferers enrolled, the per protocol (PP) populace, the mean age, the dosing routine, the price of gastroesophageal reflux episodes (GER) in the PP populace, the acid reflux disease time, the drug-related destructive events (AEs), the severe AEs, the severe drug-associated AEs, and mortality. Any disagreements in extracted information among the 2 reviewers have been resolved by way of discussion amongst all the authors.

Quality Assessment

We assessed the methodological nice of RCTs the use of the Jadad standards. Three gadgets had been considered for the Jadad scale: (1) whether or not the observe became described as randomized; (2) whether or not the study became described as doubled-blind; (three) whether or not a description of drop-outs and withdrawals become supplied. One factor became offered for every of those objects that had a positive solution. One point became provided to the examine if the randomization system changed into taken into consideration suitable, and one point become deducted if the randomization procedure became considered insufficient. Similarly, one point became offered to the study if the blinding turned into considered appropriate, and one point was deducted if the blinding become taken into consideration inadequate. Five points have been the maximum rating that would be assigned to a tribulation, and scores higher than 2 had been deemed to be indicative of ok methodological high-quality [24–26].

Statistical Analysis

This meta-evaluation became executed the usage of Review Manager five.1, which become supplied with the aid of Cochrane.Org. Meta-analysis techniques had been used to combine information acquired from separate trials. Results have been pooled for sufficiently similar results and homogeneous data (which had been decided by using the degree of statistical heterogeneity). The $\chi 2$ check turned into used to evaluate statistical heterogeneity between trials, with importance seemed as a P fee = zero.10.

For dichotomous statistics, the Mantel-Haenszel constant-outcomes model changed into used to calculate the pooled odds ratio and ninety five% self belief periods (CI) while there was no statistically big heterogeneity among the blanketed trials (heterogeneity). When heterogeneity of and % turned into discovered the various protected research, a random-impact's version turned into chosen. If there has been no heterogeneity detected via this method, the I2 test turned into used. If the heterogeneity of % was obtrusive, the inferior great study was excluded from the meta-evaluation.

Results

Study Selection Process

We diagnosed 121 articles via database searching after utility of our standards. Two statistics had been excluded because of duplication. Of the final 119 articles, nine [12–20] RCTs were selected for meta-evaluation primarily based on the inclusion standards. The seek technique is summarized in Figure 1. The identical searching outcomes have been reached by way of the 2 impartial reviewers

Study Characteristics

All nine trials had been double-blinded RCTs, and four of them had been crossover research. The trials decided on for this look at had been carried out in number one and secondary care settings in unique countries and represented a total of 283 GERD patients and healthful subjects. One trial assessed baclofen as an "upload on" therapy to proton pump inhibitors [12], however the different nine trials assessed baclofen as an character remedy. One trial adopted a prodrug of the energetic R-isomer of baclofen. Because the mechanism of motion is identical, that observe turned into also protected [13]. The subjects within the research had nonerosive reflux sickness, hypersensitive esophagus, or useful heartburn, all of which signify GERD. Most patients were adults in their 40s (besides for 30 youngsters of their 10s). The remedy duration varied from 12 h to 4 weeks in line with the designs for every trial. The information of the 9 RCTs, which includes observe layout, parameters evaluated, range of sufferers, mean age, observe duration, and dosing regimens, are summarized in Table 1.

Reduction in the Incidence of GER

Data concerning the impact of baclofen on the occurrence of GER within the PP group had been furnished by using eight of the 9 RCTs. Data for nonerosive reflux disorder, hypersensitive esophagus, and functional heartburn had been measured via pH metry, manometry, and symptom evaluation, respectively. We determined a statistically sizable difference inside the discount in GER incidence between baclofen-treated and placebo-treated topics (standardized imply distinction [SMD]: –zero.65; ninety-five % CI: –0. Ninety-four, –0.36;); furthermore, the statistical heterogeneity became insignificant (%;)

The Acid Reflux Time in the PP Population Who Were Given Either Baclofen Or Placebo for the Treatment of GERD

Data regarding the effect of baclofen on the acid reflux time in the PP institution have been furnished by six of the nine RCTs [13–16, 18, 20]. We recognized a statistically sizeable distinction between baclofen and placebo (SMD: −1.14; 95% CI: −1.Seventy two, −0.Fifty six;), and the statistical heterogeneity became insignificant (= 35%;) (Figure 3). These results provide affirmation that baclofen decreases the acid reflux time for GERD patients.

The Rate of TLESR in the PP Population Who Were Given Either Baclofen Or Placebo for the Treatment of GERD

Data concerning the impact of baclofen on the prevalence of TLESR within the PP organization have been furnished through 3 of the nine RCTs [17–19]. A statistically substantial difference became detected among baclofen- and placebo-handled subjects for decreasing the price of TLESR (SMD: −three.65; ninety five% CI: −four.30, −three.00;), and the statistical heterogeneity turned into insignificant (%;) (Figure 4). These effects verify that baclofen decreases the prevalence ofTLESR.

Side Effects in the PP Population Who Were Given Either Baclofen Or Placebo for the Treatment of GERD

Data for the general unfavourable activities of baclofen and placebo inside the PP institution were supplied with the aid of all nine RCTs. There changed into no statistically big difference inside the frequency of overall AEs among subjects given baclofen and people given placebo (OR = 1.62; 95% CI: 1.03–2.Fifty four;), and the statistical heterogeneity became excessive (= 63%,) (Figure 5). Associated mortality become now not discovered in any of the nine RCTs protected in this analysis. All aspect outcomes pronounced inside the studies have been of moderate-to-mild depth. Mental/neurological signs (dizziness, tiredness, sleepiness, and lodging disease) had been most normally pronounced as a side impact. Other mentioned aspect outcomes were stomach court cases (pain, nausea, diarrhea, and flatulence) and ache (headache, muscular). These effects propose that baclofen does now not drastically boom the quantity of Aes.

Discussion

Summary of Main Results

This meta-analysis presents rather statistical confirmation that baclofen is effective for the relaxation of GERD-associated signs. Baclofen treatment became associated with a enormous reduction inside the range of GER episodes, the acid reflux time, and the occurrence of TLESR. Our meta-analysis also demonstrated that there may be no statistically enormous distinction within the prevalence of the overall detrimental occasions between baclofen- and placebo-dealt with subjects and that the drug changed into nicely tolerated.

Applicability of the Evidence

All trials protected within the meta-evaluation furnished express data approximately the forms of

GERD-associated symptoms (the prevalence of TLESR, GER, gastric emptying, pharyngeal swallowing, and decrease esophageal sphincter stress and the acid reflux time). The imply occurrence of TLESR and GER and the acid reflux disorder time were reduced amongst research through extraordinary remedy. When meta-analysis was performed to verify the efficacy of baclofen on GERD-associated signs, the imply differences between baclofen and placebo have become smaller, however more statistical significance changed into achieved (SMD: –zero.65; ninety five% CI: –0.94, –zero.36;), (SMD: –1.14; ninety five% CI: –1.72, –zero.Fifty six;), and (SMD: –3.Sixty five; 95% CI: –four.30, –3.00;). Therefore, the meta-evaluation provides extra reliable information to assist the high-quality consequences of baclofen.4.3. Agreements and Disagreements with Other Systematic Reviews

A thorough literature seek located another overview of baclofen for the remedy of GERD [26], which became a scientific evaluate, rather than a meta-analysis, and blanketed best five research on baclofen for the remedy of GERD with best grownup sufferers. This evaluate concluded that baclofen produces statistically tremendous reduction in diverse objective measures of reflux however isn't always associated with symptomatic improvement and produces mild damaging results.

Given that nine RCTs have been blanketed on this meta-evaluation and that the evidence to support the effects of baclofen was decided in comparison to placebo, in place of energetic controls, we conclude that baclofen might be effective within the brief time period. Unfortunately, with regard to lengthy-time period efficacy, our meta-evaluation does not allow for conclusions.

Strengths and Weaknesses

Many research have proven that baclofen can lessen GER episodes [27, 28] and decrease the acid reflux disease time and the prevalence of TLESR [29, 30] in regular individuals and sufferers with GERD. The mechanism of movement of baclofen in lowering reflux entails the inhibition of TLESR, which isn't like proton pump inhibitors that lessen reflux with the aid of inhibiting acid secretion [31–33]. The relaxation of the decrease esophageal sphincter is one of the number one causes of reflux activities [34–36]. The impact of baclofen in decreasing reflux can final almost 24 h. Therefore, baclofen has already been advised as a primary or adjunct treatment for GERD [37, 38], especially for sickness that has didn't reply to proton pump inhibitors and histamine kind 2 receptor antagonists. This meta-evaluation is the first to pool scientific information from severa double-blinded RCTs on baclofen for the treatment of GERD and to research the efficacy and safety of baclofen. It will provide useful reference records for clinical practice.

There are several weaknesses of our meta-analysis that have to be taken into account when we examine the results. First, the look at's primary hassle is the paucity of eligible trials, which prohibited further subgroup analyses. Second, maximum of the studies blanketed in this take a look at had negative methodological pleasant

and/or small pattern size. Finally, additional studies comparing baclofen to different active treatments and with enormous sample length are urgently needed.

Conclusions

Although there are a few boundaries of this meta-analysis, treatment with baclofen became validated to noticeably result in the development of GERD-associated signs. Moreover, compared with placebo, baclofen did not increase the range of extreme detrimental occasions in patients with GERD. Additional nicely-designed RCTs are had to verify these conclusions.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Figure 1: Flow diagram showing the procedure for the systematic review of studies for meta-analysis.

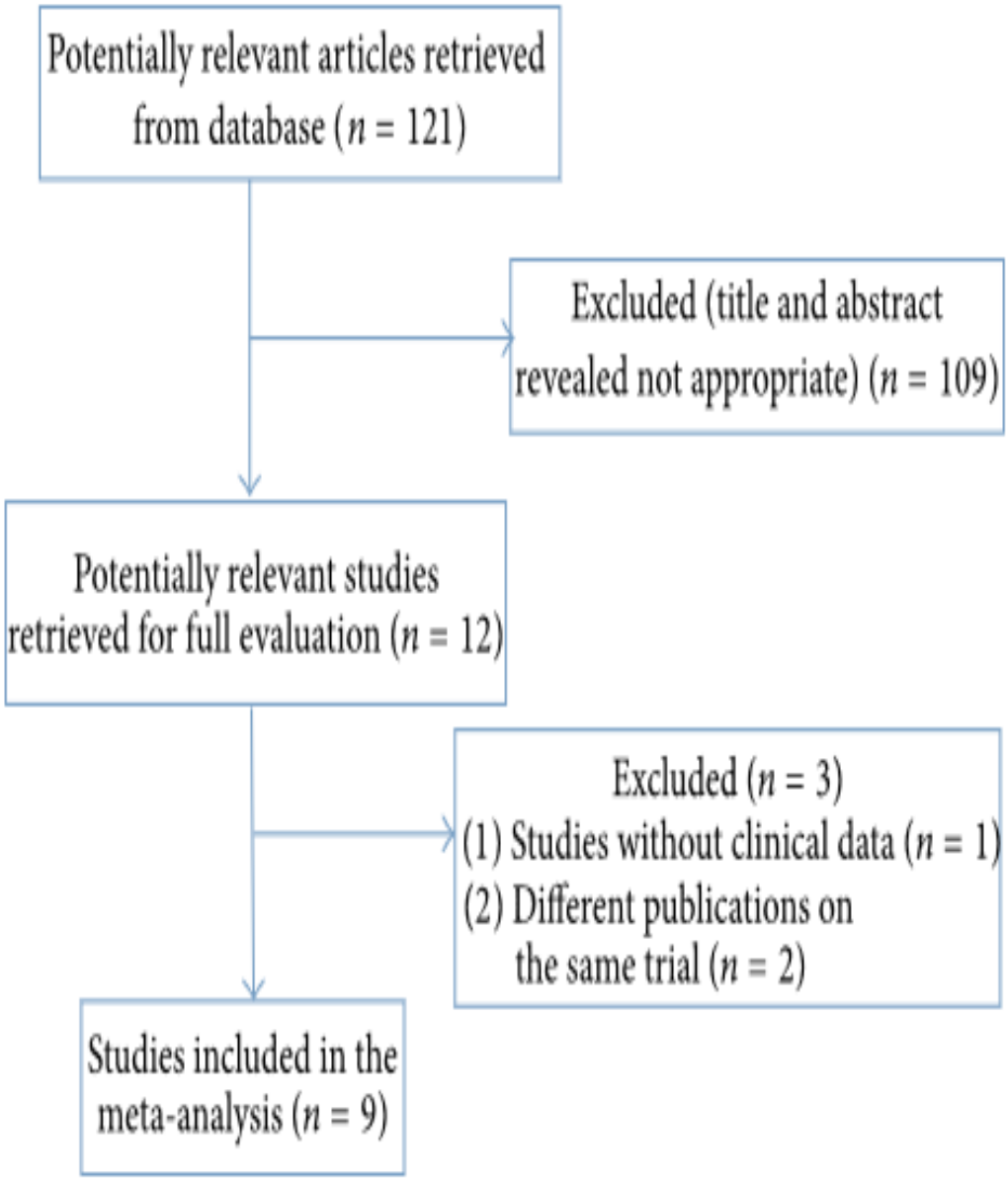

Table 1: Characteristics of the baclofen studies included in this meta-analysis.

Source	Randomization	Blinding	Withdrawals and dropouts	Jadad score
Beaumont and Boeckxstaens (2009) [12]	1	1	1	3
Cange et al. (2002) [13]	1	1	1	3
Ciccaglione and Marzio (2003) [14]	1	2	1	4
Cossentino et al. (2012) [15]	2	2	1	5
Gerson et al. (2010) [16]	2	2	1	5
Grossi et al. (2008) [17]	1	2	1	4
Lidums et al. (2000) [18]	1	1	1	3
Omari et al. (2006) [19]	1	2	1	4
van Herwaarden et al. (2002) [20]	1	1	1	3

Figure 2. These results provide confirmation that baclofen is effective in reducing the incidence of GER.

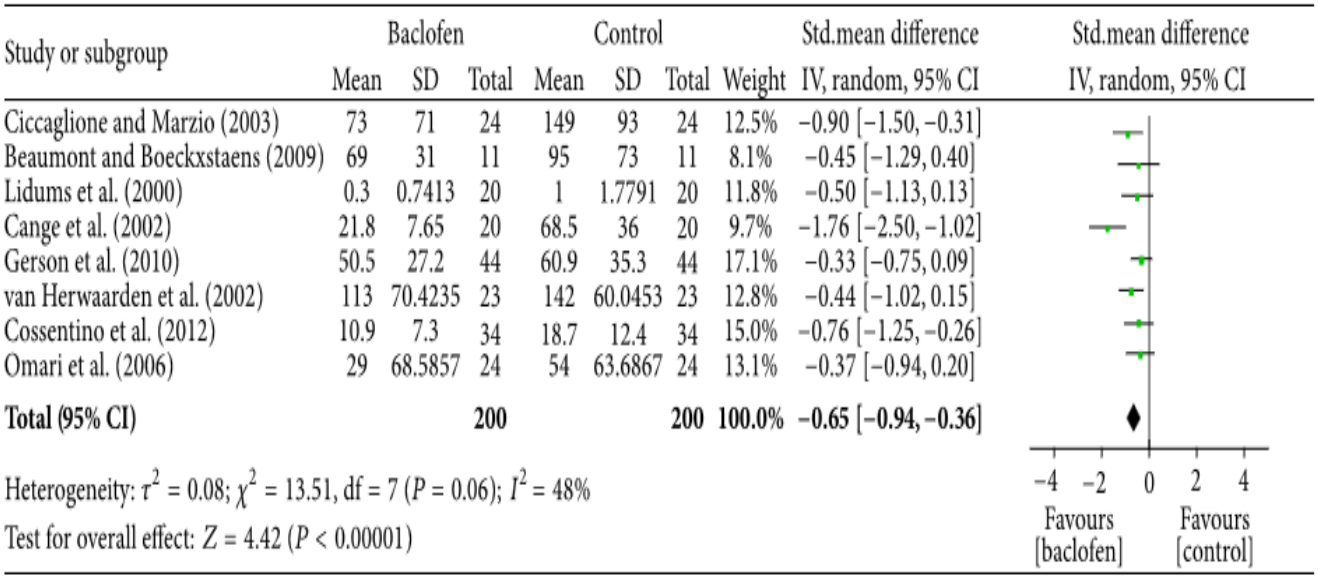

Figure 2: Meta-analysis of the incidence of GER in the PP population given either baclofen or placebo for the treatment of GERD.

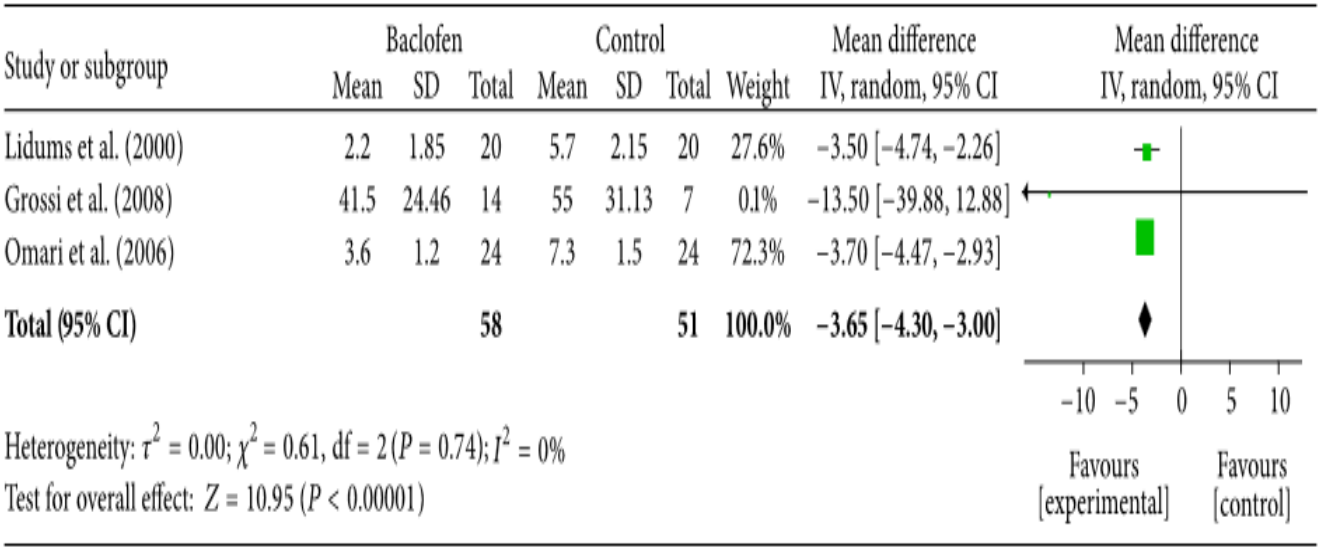

Figure 4: Meta-analysis of the incidence of TLESR in the PP population given either baclofen or placebo for the treatment of GERD.

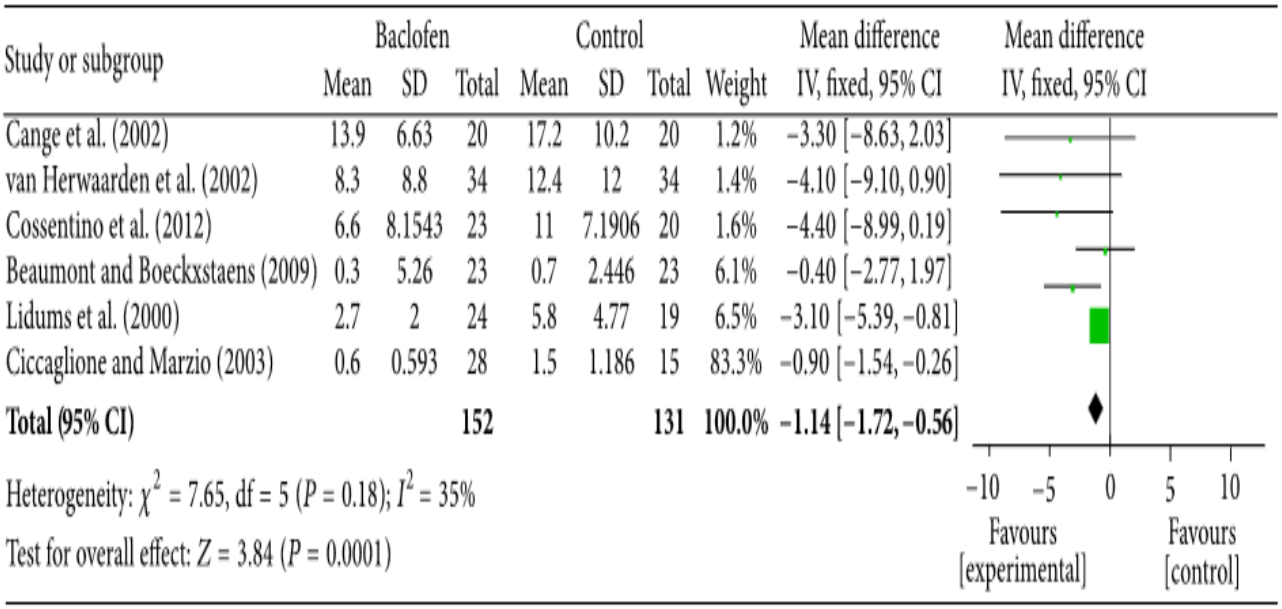

Figure 3: Meta-analysis of the acid reflux time in the PP population given either baclofen or placebo for the treatment of GERD.

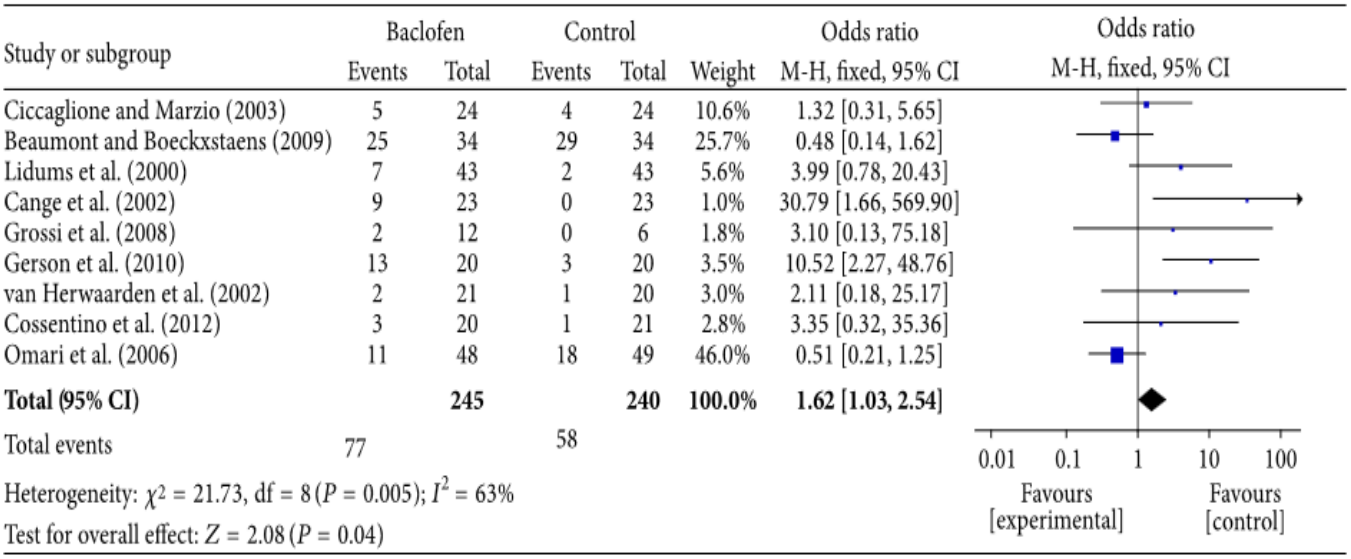

Figure 5: Meta-analysis of the overall adverse events in the PP population given either baclofen or placebo for the treatment of GERD.