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Mucosal Protective Compounds in the Treatment of Gastroesophageal Reflux Disease. A Position Paper Based on Evidence of the Romanian Society of Neurogastroenterology

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ABSTRACT

Background & Aims: Gastroesophageal reflux disease (GERD) therapy is challenging and suppression of acid secretion or prokinetics do not cure all cases. Some drugs with protective action on the esophageal mucosa have been used alternatively or in association with proton pump inhibitors (PPIs) and/or prokinetics. The Romanian Society of Neurogastroenterology undertook an Evidence-Based analysis, from which this position paper evolved.

Methods: We performed a systematic literature search in PubMed until October 2015, using the terms: sucralfate, guaiazulene, gaiazulene, dimethicone, alginate, antacids and gastroesophageal reflux. Forty-seven papers were included and analyzed. Several statements were elaborated regarding the use of these drugs in GERD. The evidence and recommendations were discussed between the authors.

Results: There is evidence in the medical literature suggesting the benefit of these drugs in GERD. In patients with persistent or mild reflux symptoms antacids rapidly relieve heartburn. Alginate-antacid combination is superior both over placebo and antacids to treat mild reflux symptoms, and can be used to treat persistent reflux symptoms despite acid suppressant therapy. Sucralfate is superior over placebo in alleviating GERD symptoms and can be used as maintenance therapy. Guaiazulene-dimethicone improves the quality of life in patients with GERD.

Conclusions: Drugs used to protect the esophageal mucosa against acid are useful in alleviating chronic heartburn, especially in patients with mild reflux symptoms.

Key words: gastroesophageal reflux disease – antacids– alginate– sucralfate – guaiazulene.

Abbreviations: CS: Chondroitin sulfate; DA: Double Action; EE : Erosive esophagitis ; GERD: Gastroesophageal reflux disease; HA: Hyaluronic acid; H2RA: Histamine 2 receptor antagonist; ITT: Intention to treat; IM: Irsogladine maleate; NERD: Non-erosive reflux disease; PPIs: Proton pump inhibitors; RCT: Randomized controlled trial; RDQ: Reflux disease questionnaire; QoL: Quality of life.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is the result of gastric content reflux in the esophagus, leading to troublesome symptoms that alter the quality of life (QoL) or determine complications [1]. The prevalence of GERD is very high in Western countries, ranging from 10 to 20%. However, when endoscopy is performed, less than 30% of patients have erosive esophagitis (EE) [2]. Over the past 40 years the clinical spectrum of GERD has evolved. GERD symptoms with normal esophageal mucosa require further investigations, such as ambulatory pH-metry or ambulatory pH-impedance, to establish whether the patient has non-erosive reflux disease (NERD), hypersensitive esophagus or functional heartburn. Only patients with increased esophageal acid exposure ("true" NERD) and those with normal esophageal acid exposure whose symptoms correlate with acidic reflux episodes (i.e. hypersensitive esophagus) will respond to gastric acid suppression, such as proton pump inhibitors (PPIs) [3, 4]. Unfortunately, even in these cases PPIs are not always efficient [3]. On the other hand, 25-47% of the patients with GERD have a moderate to poor compliance (less than 80% intake of prescribed dose) to PPIs [5], while only 27% of GERD patients dose their PPIs correctly [6]. Obviously, patients with hypersensitive esophagus to non-acid reflux and patients with

functional heartburn (i.e. normal esophageal acid exposure and no correlation between reflux events and reflux symptoms) will be resistant to PPIs [3, 4].

Most patients with GERD are treated empirically by their family physician, with acid suppression treatment with PPI or a histamine 2 receptor antagonist (H2RA), without the knowledge of the presence of erosions on esophageal mucosa [7]. Very often reflux symptoms are intermittent and self-medication based on an initial prescription is common.

The purpose of GERD treatment is first to relieve symptoms, and then to heal esophageal mucosa and to prevent complications. One of the possibilities to achieve these goals is to reduce the aggressiveness of refluxed gastric contents. PPIs are currently the most effective drugs for healing EE [8]. However, PPIs have side effects and there are some drug interactions which need to be considered especially in the elderly. In addition, some authors recommend a "step-up" approach in the management of NERD patients, with PPIs at the top of this strategy. H2RAs and mucosal protective compounds (sucralfate, guaiazulene, alginates, and antacids), were developed decades ago, but there are still some indications for their use: patients with mild GERD symptoms (less than once a week) and no EE [9].

Transient lower esophageal sphincter relaxation is the main mechanism of gastro-esophageal reflux. Other factors involved in the pathogenesis of GERD are impaired esophageal clearance [10], decreased salivary secretion [11], reduced number of pharyngeal swallows during reflux episodes [12], and delayed gastric emptying [10]. The rationale of using mucosal protective compounds in GERD relies on the observation that esophageal mucosal defense plays a role in the pathogenesis of GERD. Esophageal epithelium with stratum corneum provides defense as a permeability barrier. The cells have an acid buffering and acid transport properties, all these functions being maintained by an adequate blood supply [13].

The aim of this position paper was to gather Romanian experts' opinion on the usefulness and indications of these non-anti-secretory drugs in the treatment of GERD. This document should be a useful tool for primary care physicians and for specialists.

METHOD

We performed a systematic literature search in PubMed until October 2015, using the following terms: "sucralfate and reflux", "guaiazulene and reflux or gaiazulene and reflux", "dimethicone and reflux", "alginate and reflux" and "antacids and gastroesophageal reflux". We limited our research to articles published in English, French and German, conducted on human subjects, and with available abstracts. References of relevant articles were manually searched to find papers not returned by our search strategy. Our initial search returned 864 titles and in the end 47 papers (including meta-analyses and systematic reviews) were used for the elaboration of this paper.

Based on available data in the literature, several statements were developed regarding the use of these drugs in GERD, and were sent by e-mail to all experts authors, who were asked to vote using a six-point Likert scale: (1) agree strongly, (2) agree with minor reservation, (3) agree with major reservation, (4) disagree with minor reservation, (5) disagree with major reservation, and (6) disagree strongly. Consensus was defined a priori as > 70% agreeing strongly or with minor reservations with a statement. The level of evidence and grade of recommendation were discussed between the authors, using the Oxford evidence criteria (Table I) [14]. The strength of the evidence was classified according to the GRADE system. Quality of evidence was graded as high, moderate, low and very low [15].

Table I. Grade of recommendation according to Oxford criteria

Grade of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation

In the end we included a short narrative paragraph regarding other mucosal protective compounds, which are not available in Romania.

RESULTS

Use of antacids in GERD

The most widely practiced management strategy for symptomatic GERD is to reduce gastric acidity, and thereby the exposure of esophageal mucosa to gastric acid during episodes of reflux [3]. One option to reduce gastric acidity is the use of antacids, mainly for mild GERD symptoms. Antacids contain a combination of magnesium trisilicate, aluminium hydroxide or calcium carbonate, with a net effect of reducing gastric acidity and peptic activity. In addition, aluminium containing antacids accelerate the healing of gastroduodenal ulcerations, due to a cytoprotective activity resulted from the enhancement of natural mucosal defense mechanisms. This dose dependent protective activity remains after acidification, i.e. after loss of acid neutralizing capacity. The active component of aluminium containing antacids is $Al(OH)_3$ which activates the nitric oxide system, and subsequently increases the mucosal microcirculation [16]. Some studies have reported that aluminium containing antacids increased prostaglandin formation in gastric mucosal tissues and enhanced secretion of prostaglandins into the gastric lumen [17]. These results were not confirmed in other studies [18].

Antacids provide relief of heartburn within 5 minutes, but their effect is very short (30 to 60 minutes) [9].

Three randomized controlld trials (RCTs) compared antacids (aluminum hydroxide/magnesium carbonate, and magnesium/aluminum hydroxide) with placebo [19-21]. In one double-blind crossover RCT in 47 patients with reflux esophagitis, antacids reduced the global symptomatic scores, the episodes of regurgitation and episodes of heartburn

during night and day [19]. Simon et al. compared antacid (113 patients) and placebo (111 patients) and concluded that antacid relieved 62% of heartburn episodes, while placebo relieved 41% of heartburn episodes ($p<0.05$). Antacids provided more rapid and more frequent relief than placebo (OR = 1.57 vs. 1, $p<0.003$). One third of patients in the antacid group and 43% in the placebo group used rescue antacids ($p<0.05$) [20]. The third trial included only 32 patients and found no significant difference in heartburn frequency or severity between an antacid (Maalox) and a placebo [21].

In the meta-analysis of Tran et al., 4 trials comparing antacids (578 patients) and placebo (577) were analyzed. Subjective improvement after 2 and 4 weeks of treatment was evaluated. There was a trend favoring antacids over placebo, but the combined absolute benefit increase of antacids over placebo was only 8% (95% CI: 0-16%, $p=0.06$). The combined relative benefit increase was 0.11 (95% CI: 0.03-0.20), and number needed to treat was 13 (95% CI: 6-250) [22].

Antacids seem not to be very effective when compared with placebo for symptom relief. However, several studies showed that in NERD patients, they are at least as effective as H2RAs for up to 3 hours [23-25]. One large double-blind, 3-fold cross-over RCT (including 562 patients with GERD symptoms) compared a single dose of 1000 mg of hydrotalcite (aluminium–magnesium-hydroxide–carbonate) with 10 mg of famotidine or placebo (as on-demand treatment of heartburn) and showed that hydrotalcite significantly decreased heartburn severity after 10 minutes (when compared with placebo), and had better efficacy at 30 minutes and 3 hours after intake, in comparison with famotidine or placebo [24]. Another study concluded that hydrotalcite is a good option for on-demand therapy for NERD patients, due to its cost-effectiveness (1/3 of the costs using esomeprazole on-demand) and rapidity of action [25].

Antacids are fast and effective at relieving reflux symptoms. However, when used excessively and for long periods of time, side effects are not negligible. Aluminum containing antacids can cause constipation and binds phosphate in the gut, leading to hypophosphatemia, metabolic bone disease, neurotoxicity, and anemia. Several side effects (such as hypercalcaemia, milk–alkali syndrome or constipation) can also be observed with calcium-antacids, but not at the recommended doses. Overdose/repetitive use of magnesium-containing antacids can cause hypermagnesaemia, which could be fatal [26].

Regarding the use of antacids in pregnant women, the data comes mainly from the experts' consensus and reviews. A recent meta-analysis identified only one trial that evaluated the effect of magnesium and aluminum hydroxide plus simethicone (liquid and tablet) compared with placebo, for relieving heartburn in pregnancy. Women who received the treatment reported complete heartburn relief more often than women receiving no treatment or placebo (RR 1.85, 95% CI 1.36-2.50), without a clear difference in the rate of side effects (RR 0.63, 95% CI 0.21 to 1.89) [27]. From the experts' consensus, calcium or magnesium containing antacids are preferred, because there are data showing that women with an adequate calcium intake are at a reduced risk of developing hypertension and pre-eclampsia during pregnancy [28]. Magnesium sulfate supplementation reduces the risk of eclampsia by 50% compared with placebo [29]. So both supplementation with calcium and magnesium (absorbed from antacids) are considered to have beneficial effects in pregnant women, and are therefore preferred in the treatment of heartburn in pregnancy. The antacids should be used 'on demand' and the recommended doses should not be surpassed.

There is some evidence to support the efficacy of antacids over placebo in GERD. Antacids offer a rapid relief of symptoms, are not expensive, and therefore may be used by patients with mild intermittent reflux symptoms. Antacids may be used for persistent GERD symptoms despite acid suppressant therapy. Based on these data, our recommendations are summarized in Table II.

Use of raft-forming agents in GERD

One of the concepts in GERD pathogenesis, mainly in the pathogenesis of postprandial reflux, is that of the gastric acid pocket, defined as the postprandial highly acidic proximal stomach [30]. The presence of this gastric acid pocket has become an attractive therapeutic target. Alginate, a polysaccharide derived from seaweed, binds water in the acid pocket and forms a viscous gel, displacing the acid pocket distally, below the diaphragm in 70% of patients [31]. The bicarbonate added to alginate is converted to carbon dioxide which forms bubbles which are trapped within the gel and convert it to a lighter substance that can rise to the surface of gastric contents and float (thus the name "raft-forming agent") [32]. The exact mechanism of action of alginate-

Table II. Recommendations of the Romanian Society of Neurogastroenterology concerning the use of antacids in gastroesophageal reflux disease

Statement	Experts agreement	Level of evidence	Grade of evidence	Grade of recommendation
Antacids are slightly superior over placebo in treating heartburn	91.6%	2a	Low	B
Antacids may be used to rapidly relief uncontrolled GERD symptoms	91.6%	2b	Moderate	B
Antacids may be used as over-the counter drugs, to treat mild or infrequent reflux symptoms, especially in NERD patients who choose to self-medicate	83.3%	2b	Low	B
Antacids (calcium or magnesium-containing antacids) can be used in pregnant women with GERD symptoms.	91.6%	4	Very low	C
In pregnant women, there is no clear difference in the rate of side effects between antacids and placebo.	83.3%	4	Very low	C

GERD: Gastroesophageal reflux disease, NERD: Non-erosive reflux disease

antacid combination in GERD is not well established; several studies using alginates addressed this topic but the results are inconsistent. The common assumption is that alginate-antacid combination creates a mechanical barrier to acid reflux as it moves into the esophagus ahead of acidic gastric content and prevents reflux [3]. Recent data showed that although alginate-antacid reduced distal esophageal acid exposure it did not influence the number of reflux events (acid or weakly acidic). Therefore, it seems that alginate–antacid effect relates to displacement and neutralization of the postprandial gastric acid pocket, rather than preventing reflux [33]. On the contrary, another small study that compared pre and postprandial esophageal pH-multichannel impedance parameters, showed that alginate decreased significantly the number of acid reflux events, the percentage time pH<4.0 and the height of proximal reflux compared with baseline [34]. Alginate, pectin and carbenoxolone are raft-forming agents. Alginate preparations are extensively studied, and are available in Romania, marketed as Gaviscon.

Alginate/antacid combination versus placebo

We identified three placebo-controlled trials assessing alginates efficacy in GERD. The most recent (2015) and largest RCT on this subject included 1107 GERD patients [intention to treat (ITT) population, 1073]: 536 patients in the Gaviscon Double Action (DA) group and 537 patients in the placebo group. Reflux disease questionnaire (RDQ) symptom score before and after a 7-day treatment was used to assess the efficacy of Gaviscon DA. There was a substantial placebo response. However, Gaviscon DA was superior to placebo in reducing RDQ score for GERD dimensions (from 2.51 at baseline to 1.25 after treatment for Gaviscon DA, and from 2.50 to 1.46 for placebo, p<0.001). Ninety percent of patients in DA group, and 84% in the placebo group experienced symptom improvement [35]. Another RCT included 110 GERD patients. Gaviscon DA decreased reflux symptoms and the overall RDQ symptom score. The overall treatment response was higher in the Gaviscon group than in the placebo group (4.1 vs. 1.9, p<0.001) [36]. The third double-blind parallel-group RCT included 100 patients with GERD (ITT population, 94) and showed that sodium alginate was assessed as superior to placebo, both by investigators and patients at week two and week four [37]. In the meta-analysis of Tran et al. (2007), four RCTs were analyzed (including 146 patients in the treatment group and 138 patients in placebo group). The combined absolute benefit increase of alginate/antacid combination versus placebo was 26% (CI 95%: 12-41%, p<0.0001), and the relative benefit increase was 0.60 (95% CI: 0.25-0.91). The NNT was 4 (95% CI: 2-9) [22].

Alginate antacids versus antacids

Several studies compared the clinical efficacy and safety of alginate-antacid and antacids alone. Studies from the 70's showed that alginate and standard antacid were equally effective in reducing the number of heartburn episodes [38] and determined clinical improvement in the majority of patients [39]. One open-label, prospective, randomized, parallel group clinical trial included 203 GERD patients, and randomized 191 patients (only patients with symptoms in the run-in period) to a 14-day treatment with either drug. Sodium alginate was faster than magaldrate (hydroxymagnesium aluminate complex) in relieving GERD symptoms. The duration of action and the efficacy were slightly better for alginate; 81.6 % of patients in the sodium alginate group and 73.9% of patients in the magaldrate group reported total disappearance of symptoms, but without reaching statistical significance. Two events in the sodium alginate group (diarrhea and nausea) were considered to be potentially drug-related [40]. Another study randomized 134 NERD patients to receive alginate-antacid or antacid (Nacid®) for a 6 weeks period and showed a greater reduction in the severity (P < 0.0001) and frequency (P = 0.0015) of heartburn at 6 weeks, and a lower frequency of heartburn, regurgitation and belching at 3 weeks. The improvement in the QoL was more remarkable in the alginate-antacid group. The adverse events were similar in both groups, two patients in the alginate-antacid group reporting constipation [41].

Alginate/antacids versus PPIs

Several studies compared the efficacy of sodium alginate with different PPIs. One study that included 195 NERD patients, compared alginate suspension (20 ml three times a day) with omeprazole (20 mg/day) and showed that 53.3% of patients achieved adequate heartburn and regurgitation relief compared to 50.5% of patients in the omeprazole group (p=0.175) after 4 weeks of treatment. More than 86% of patients graded the overall satisfaction using one of these treatments as 'good' or 'very good'. The authors concluded that sodium alginate was as effective as omeprazole for symptomatic relief in NERD patients [42]. In addition, adding sodium alginate to omeprazole may increase the rate of NERD patients with a complete resolution of heartburn. A study that included 76 NERD patients reported a complete resolution of heartburn in 56.7% of patients in combination group vs. 25.7% in omeprazole group alone. The heartburn-free days also increased in combination group [43]. In another study, the authors compared the short-term efficacy (at day 7 and day 14) of Gaviscon 10mL, 4 times a day (120 patients) with omeprazole 20mg/day (121 patients) in a randomized double-blind, double-dummy trial. With both treatments the mean time to onset of the first 24-h heartburn-free period after initial dosing was 2 days (± 2.2). The omeprazole group had a higher mean number of heartburn-free days by D7 (3.7 ± 2.3 days vs. 3.1 ± 2.1; p = 0.02), and a better relief of pain (p=0.049) [44].

Alginates in pregnancy

Few studies have investigated the safety and efficacy of alginates in the treatment of heartburn in pregnancy. Half of the 150 pregnant women instructed to take Gaviscon 5-10 ml when necessary reported rapid heartburn relief (within 10 minutes), and 88% rated drug's efficacy as "very good". No safety concerns for the mother or the fetus were reported in this study [45]. In another study, 50 pregnant women (during the 2nd and 3rd trimester of pregnancy) with gastroesophageal reflux symptoms were treated for 1 month with Gaviscon (2 tablespoons after each meal and at bedtime). All symptoms improved after 1 month; 98% of women considered that the drug is efficient, and no side effects were noted [46]. Some adverse effects of alginates were reported, mainly related

Table III. Recommendations of the Romanian Society of Neurogastroenterology concerning the use of alginate-antacid combination in gastroesophageal reflux disease

Statement	Experts agreement	Level of evidence	Grade of evidence	Grade of recommendation
Alginate-antacid is superior over placebo in the treatment of GERD symptoms	100%	1b	Moderate	A
Alginate-antacid combination can be used to manage mild symptoms of reflux, especially in NERD patients	100%	2b	Low	B
Alginate-antacid combination is more effective than antacids for the treatment of symptoms in NERD patients	100%	2b	Low	B
Alginate–antacid combination is as effective as Omeprazole 20 mg/day in patients with mild GERD symptoms, especially in NERD patients	83.3%	2b	Low	B
Alginate-antacid combination may be used in pregnant women with heartburn	100%	3b	Very low	B
Alginate-antacid combination may be used to treat persistent reflux symptoms despite acid suppressant therapy	83.3%	2b	Very low	B

GERD: gastroesophageal reflux disease, NERD: Non-erosive reflux disease

with the antacid included in the preparation (i.e. magnesium trisilicate or sodium bicarbonate). Therefore, some authors suggested that alginates combined with these antacids should be avoided during pregnancy due to adverse events if used long-term and at high doses [47].

Alginate-antacid combination is superior both over placebo and antacids alone in alleviating heartburn in GERD patients. This combination proved similar efficacy as compared to a single dose omeprazole, especially in NERD patients. Alginate-antacid can be added to PPI treatment in case of persistent symptoms, leading to a further improvement of symptoms (Table III).

Use of Sucralfate in GERD

Sucralfate is a salt of sucrose sulfate and aluminium hydroxide, which binds to the mucosa creating a physical barrier that blocks the diffusion and interaction of hydrochloric acid, pepsin or bile salts and esophageal mucosa [48]. The affinity of sucralfate for inflamed mucosa is explained by the formation of polyvalent bridges between the negatively charged sucralfate polyanions and positively charged proteins present in mucosal lesions [49]. It also has cytoprotective properties attributed to the fact that sucralfate increases the local levels of fibroblast growth factors and induces a rise of prostaglandins in the mucosa, thus inducing mucosal healing [50]. Sucralfate (1g qid, for 3 months) normalizes esophageal acid clearance rate suggesting that once the inflammation subsides, esophageal motor function is restored [51]. In addition, sucralfate adsorbs pepsin and bile salts, resulting in a comprehensive defense against several aggressive factors [49].

Several RCTs argued the superiority of sucralfate versus the placebo in alleviating GERD symptoms. We identified four RCTs, with variable doses (1g bid to 1g qid) and durations of treatment (6, 8 or 12 weeks) that proved some benefit of sucralfate over placebo in improving GERD symptoms and endoscopic aspect of esophageal mucosa. However, in two of these studies statistical significance was not achieved. One study (141 NERD patients, 1g sucralfate gel bid for 6 weeks), showed a "good" or "excellent " overall response in 45% of patients in the active group, compared with 22% in the placebo group ($p<0.001$) [52]. In another study (36 patients with severe EE), sucralfate (1g after meals and 2g at bed time) or placebo were added to cimetidine (300mg qid) for 12 weeks. The combination of cimetidine and sucralfate was superior to cimetidine alone in improving daytime heartburn and overall endoscopic outcome, without statistical significance regarding endoscopic healing [53]. In another two studies (that included 68 and 138 patients, respectively) the proportion of patients with symptomatic or endoscopic improvement was higher after sucralfate treatment, but not significantly when compared with placebo [54, 55]. A meta-analysis published in 1987 (including 51 double blind RCTs) concluded that sucralfate was better than placebo in improving esophagitis endoscopic lesions. More recently, in 2005, a meta-analysis confirmed the superiority of sucralfate over a placebo as the maintenance therapy of GERD [56].

Sucralfate seems to be equally efficient with H2RAs in improving GERD symptoms, and also in determining mucosal healing. At the end of the 80's it was considered a safe alternative to H2RAs in GERD patients. We identified 8 studies (in adults) that compared sucralfate and ranitidine or cimetidine, the majority of them in EE, the endpoint of the trials being mucosal healing. In one study, monotherapy with sucralfate in milder forms of EE was comparable with the combination of sucralfate during the day and ranitidine after dinnertime [57]. In another study, endoscopic healing was observed in 47% on sucralfate (suspension 6g/day) and in 31% of patients receiving ranitidine (150mg bid), and healing or endoscopic improvement was observed in 81% of patients on sucralfate vs. 64% of patients on ranitidine ($p> 0.05$). Heartburn and acid regurgitation were relieved in similar proportions in both groups [58]. Complete healing of esophageal erosions with sucralfate varied from 19.4% [59] to 60% [60]. In all these studies, the duration of treatment ranged between 8 weeks and 6 months, so that tachyphylaxis commonly seen with H2RAs sometimes after only 2 weeks was not taken into account, and could partly explain the noninferiority of sucralfate.

There is conflicting data regarding the role of sucralfate in preventing the recurrence of reflux esophagitis. A double-blind

Table IV. Recommendations of the Romanian Society of Neurogastroenterology concerning the use of sucralfate in gastroesophageal reflux disease

Statement	Experts agreement	Level of evidence	Grade of evidence	Grade of recommendation
Sucralfate is superior over placebo in alleviating GERD symptoms	100%	2a	Low	B
Sucralfate is as efficient as H2RAs in improving GERD symptoms, and in promoting mucosal healing	91.6%	2b	Moderate	B
Sucralfate can be used as maintenance therapy (after healing of EE with PPIs) in order to prevent relapse of esophagitis	83.3%	2b	Very low	B
Sucralfate can be used in pregnant women with GERD symptoms	100%	2b	Low	B

GERD: gastroesophageal reflux disease, H2RA: histamine 2 receptor antagonist, EE: erosive esophagitis

RCT followed for 6 months 88 patients treated with sucralfate (2g bid) and 93 with placebo and reported a relapse rate of esophagitis of 31% in sucralfate group vs. 65% in the placebo group ($p<0.001$) [61]. Another study reported no difference between sucralfate and placebo in terms of relapse rate of esophagitis during long-term treatment [59].

The efficacy of sucralfate vs. alginate/antacid was compared in one study. Both treatments significantly improved symptoms after 6 weeks (in 70% of patients) and esophagitis healed in 53% of patients treated with sucralfate, and 34% of patients treated with alginate/antacid ($p> 0.05$) [62].

Data about the use of sucralfate in pregnancy is scarce. A RCT included 42 pregnant women and reported symptoms improvement in over 80% , without maternal or fetal adverse events [63]. In a surveillance study, among 185 newborns exposed to sucralfate in the first trimester, 5 birth defects were observed, whereas 8 were expected [47]. In a meta-analysis [27], only one study with sucralfate in pregnancy was included (n= 65). Women in the sucralfate group experienced more often complete relief of heartburn compared to women who received advice on diet and lifestyle choices (RR 2.41, 95% CI 1.42 to 4.07). The evidence on side effects rate between the two groups (RR 1.74, 95% CI 0.07 to 41.21) was not clear [27]. Sucralfate is a FDA category B drug. As sucralfate is poorly absorbed from the gastrointestinal tract, current guidelines [9] and our recommendation is that sucralfate can be used in pregnant women who experience GERD symptoms.

Sucralfate can decrease bioavailability of certain drugs (i.e. fluoroquinolones, digoxin), including some PPIs [64]. Recommending patients to dose their PPI correctly (i.e. 30– 60 min before any meal of the day) [4] and to use sucralfate after each meal (i.e. at least 1 hour after PPI ingestion) diminishes the interaction between the two drugs [64].

Sucralfate relieves GERD symptoms, can induce mucosal healing and can prevent to some extent recurrent esophagitis when used as maintenance therapy (Table IV).

Use of guaziaulene-dimethicone in GERD

Pepsane®, a combination guaiazulene (4mg)-dimethicone (3g), is currently marketed in Romania with two major indications: GERD and dyspepsia. Azulenes are widespread in nature, one of their prime sources being algae. Studies on animal models showed that azulenes have antioxidant activity, interact with membrane lipids, reduce histamine levels, and thus acid secretion in the stomach. They also have anti-inflammatory [65] and anti-oedema action, and increase the blood flow in the mucosa [66]. Dimethicone and simethicone (polydimethylsiloxane) are substances with anti-foam action, transforming small gas bubbles in larger ones which are easier to move and eliminate. This mechanism is poorly documented, but several studies showed that simethicone reduces gas related dyspeptic symptoms, and that dimethicone has a gastroprotective effect [67].

Our search identified four studies related with these two compounds. Two studies referred to dimethicone [68, 69] and both showed a potential benefit of adding dimethicone to antacids for improving both macroscopic and microscopic esophageal appearances. The combination dimethicone/antacid gel was compared with a simple antacid gel in a double-blind trial in 45 patients with reflux esophagitis. Thirty eight patients completed the 8-week course of therapy. Both treatments reduced pain scores at 4 and 8 weeks. There was a tendency for the dimethicone/antacid group to better improve esophageal inflammation [68]. The other trial compared the efficacy of dimethicone/antacid vs. alginate/antacid in 53 patients with GERD [69]. The results nearly reached statistical significance, possibly due to a type II error.

Another study was a double blind RCT of guaiazulene and dimethicone vs. placebo and effects on QoL [70]. This study was part of a phase III trial published in 2003 by Ruszniewski et al., and we contacted the manufacturer for the final article. The trial included 233 patients with moderate GERD symptoms and either NERD or grade 1 esophagitis (Savary-Miller classification). The patients were randomized to receive either Pepsane® or placebo after each meal, for 28 days. The primary endpoint of the study was a 50% reduction in the global symptomatic score, and was achieved in 54.1% of patients from the Pepsane® group, vs. 41.1% of patients in the placebo group at 14 days ($p= 0.07$). The secondary endpoints were: physicians assessment of efficacy (Pepsane® vs. placebo at 14 days - 66.7% vs. 51.7 %, $p<0.02$, but not at 28 days); global efficacy of the treatment ("clear improvement" in 52% of patients in Pepsane® group vs. 37% of patients in placebo group, $p<0.05$); tolerance and side effects were comparable between the two groups. Pepsane® significantly improved the scores of quality of life (QoL) in three dimensions [71]. After 4 weeks of treatment, QoL scores in the Pepsane® group were similar with those observed in the general population, but remained significantly lower in the placebo group [70].

Table V. Recommendations of the Romanian Society of Neurogastroenterology concerning the use of guaiazulene-dimethicone in gastroesophageal reflux disease

Statement	Experts agreement	Level of evidence	Grade of evidence	Grade of recommendation
Guaiazulene-dimethicone is slightly superior over placebo in the control of GERD symptoms	91.6%	2b	Very low	B
Guaiazulene-dimethicone is more effective than placebo in improving quality of life in GERD patients	91.6%	2b	Very low	B
Guaiazulene-dimethicone rapidly relieves heartburn	91.6%	4	Very low	C

GERD: gastroesophageal reflux disease

In an open trial involving 118 dyspeptic patients, including patients with GERD, the treatment with guaiazulene-dimethicone combination reduced the proportion of patients with heartburn, from 66% at the beginning of trial to 14% after one month of therapy. The therapeutic effect of this combination was very rapid (less than 20 minutes) in 82.2% of patients [72].

Even though these trials do not allow a definite conclusion on efficacy, they showed that Pepsane® rapidly relieves heartburn in a high proportion of patients, and improves the QoL. It could be a therapeutic option in patients with symptomatic NERD (Table V).

Drugs not available on the Romanian market

In the last decade, several compounds, already used in other diseases (i.e. gastric ulcer, bone diseases) were tested in GERD patients. To date, we have limited data on their efficacy, therefore there are no clear indications of these drugs in GERD. For example, rebamipide is a mucosal protective agent, which favors ulcer healing and prevents gastric injury through several mechanisms: induces prostaglandin synthesis, up-regulates growth factors, and has anti-inflammatory effects [73]. In animal studies, pretreatment with rebamipide significantly reduced both macroscopic and microscopic esophageal injuries and increased inflammatory mediators [74]. In humans, results published so far are contradictory [73, 75]. Irsogladine maleate (IM), an anti-ulcer treatment used in Asian countries, inhibits production of proinflammatory cytokines and reinforces gap junctional intercellular communication. NERD patients with no endoscopic abnormalities might benefit from this compound [76]. Hyaluronic acid (HA) is involved in several key processes, including cell signaling and wound repair and regeneration [77]. Chondroitin sulfate (CS) has possible benefits in inflammatory diseases [78]. Based on the natural properties of these two glycosaminoglycans, new drugs containing a combination of HA and CS were developed. On a swine model, perfusion with this combination reduced the permeability of the injured esophageal mucosa [79]. This barrier effect was also tested in 20 NERD patients, and authors reported that heartburn and regurgitation significantly improved [80].

In the end, we summarize the main recommendations of this position paper (Table VI).

CONCLUSIONS

Several therapeutic options besides PPIs are available for GERD: antacids, alginate-antacids combinations, sucralfate and guaiazulene-dimethicone. These drugs offer a rapid relief of symptoms. Sucralfate promotes mucosal healing and to a minor extent prevents recurrence of esophageal erosions. Given the limited absorption from the digestive tract, these preparations can also be used during pregnancy. The use of these drugs might also reduce the costs of treating this chronic disorder. Based on the current knowledge, mucosal protective compounds cannot replace PPIs in the treatment of GERD, but can be useful in mild cases or in PPI-refractory GERD, either alone or in combination with PPIs. There are some data suggesting that long-term use of these drugs might delay symptom relapse and prolong remission, but this remains to be proven.

Conflicts of interest: The following authors were speakers at local symposia organized by pharmaceutical companies: Reckitt Benckiser

Table VI. Synoptic table with the main recommendations of this position paper

Drug	Regimen	Effects	Indications	Level of evidence
Antacids	1-2 tablets qid (after meals and at bedtime)	Rapidly reduce heartburn; aluminium containing antacids have cytoprotective effect	Mild NERD symptoms, uncontrolled GERD symptoms in addition to PPIs	2b
Alginate-antacid	10 to 20 ml qid (after meals and at bedtime)			
	2-4 tablets qid (after meals and at bedtime)	Reduces heartburn, regurgitation and belching	NERD patients with mild symptoms	2b
Sucralfate	1 or 2 g bid to 1g qid (after meals and at bedtime), at least 1 hour after PPI ingestion	Relieves heartburn and regurgitation, promotes mucosal healing	GERD with esophagitis	2b
Guaiazulene-dimethicone	1 capsule tid, after meals *or* 1 or 2 sachets containing oral gel tid, after meals	Reduces heartburn, improves quality of life	NERD patients with mild symptoms	2b

(V. Drug, P.J. Porr, D.L. Dumitrascu), Dr. Reddy's (L. Nedelcu, P.J. Porr), Takeda (D.L. Dumitrascu, P.J. Porr), Alfa Wasserman (O. Fratila, D.L. Dumitrascu), Krka (V. Drug) and Sodimed (V. Drug and D.L. Dumitrascu). No funding was received for this manuscript. These companies were not involved at any stage in the Position Paper preparation and manuscript writing.

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REFERENCES

1. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. Lancet 2006; 367: 2086-2100. doi: 10.1016/S0140-6736(06)68932-0
2. Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. Scand J Gastroenterol 2005; 40: 275-285. doi: 10.1080/00365520510011579
3. Boeckxstaens G, El-Serag HB, Smout AJ, Kahrilas PJ. Symptomatic reflux disease: the present, the past and the future. Gut 2014; 63: 1185-1193. doi: 10.1136/gutjnl-2013-306393
4. Scarpignato C. Poor effectiveness of proton pump inhibitors in non-erosive reflux disease: the truth in the end! Neurogastroenterol Motil 2012; 24: 697-704. doi: 10.1111/j.1365-2982.2012.01977.x
5. Van Soest EM, Siersema PD, Dieleman JP, Sturkenboom MC, Kuipers EJ. Persistence and adherence to proton pump inhibitors in daily clinical practice. Aliment Pharmacol Ther 2006; 24: 377–385. doi: 10.1111/j.1365-2036.2006.02982.x
6. Gunaratnam NT, Jessup TP, Inadomi J, Lascewski DP. Sub-optimal proton pump inhibitor dosing is prevalent in patients with poorly controlled gastro- oesophageal reflux disease. Aliment Pharmacol Ther 2006; 23: 1473–1477. doi: 10.1111/j.1365-2036.2006.02911.x
7. Modlin IM, Hunt RH, Malfertheiner P, et al. Diagnosis and management of non-erosive reflux disease--the Vevey NERD Consensus Group. Digestion 2009; 80: 74-88. doi: 10.1159/000219365
8. Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev 2007; (2): CD003244. doi: 10.1002/14651858.CD003244.pub2
9. Kahrilas PJ. Medical management of gastroesophageal reflux disease in adults. In: Post TW, editor. UpToDate. Waltham, MA; 2015 [cited November 3, 2015]. Available at: http://www.uptodate.com/contents/medical-management-of-gastroesophageal-reflux-disease-in-adults
10. Farré R. Pathophysiology of gastro-esophageal reflux disease: a role for mucosa integrity? Neurogastroenterol Motil 2013; 25: 783-799. doi: 10.1111/nmo.12201
11. Campisi G, Lo Russo L, Di Liberto C, et al. Saliva variations in gastro-oesophageal reflux disease. J Dent 2008; 36: 268-271. doi: 10.1016/j.jdent.2008.01.003
12. Bremner RM, Hoeft SF, Costantini M, Crookes PF, Bremner CG, DeMeester TR. Pharyngeal swallowing. The major factor in clearance of esophageal reflux episodes. Ann Surg 1993; 218: 364-369.
13. Orlando RC. The integrity of the esophageal mucosa. Balance between offensive and defensive mechanisms. Best Pract Res Clin Gastroenterol 2010; 24: 873-882. doi: 10.1016/j.bpg.2010.08.008
14. Oxford Centre for Evidence-based Medicine – Levels of evidence (March 2009). Available at: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ (Accessed October 2015).
15. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328: 1490. doi: 10.1136/bmj.328.7454.1490
16. Konturek SJ, Brzozowski T, Majka J, Szlachcic A, Nauert C, Slomiany B. Nitric oxide in gastroprotection by aluminium-containing antacids. Eur J Pharmacol 1992; 229: 155-162. doi: 10.1016/0014-2999(92)90550-N
17. Gasbarrini G, Andreone P, Baraldini M, Bonvicini F, Cursaro C, Brocchi E. Protection of the upper gastrointestinal mucosa: the role of antacids. Int J Clin Pharmacol Res 1990; 10: 173-178.
18. Lambrecht N, Trautmann M, Korolkiewicz R, Liszkay M, Peskar BM. Role of eicosanoids, nitric oxide, and afferent neurons in antacid induced protection in the rat stomach. Gut 1993; 34: 329-337. doi: 10.1136/gut.34.3.329
19. Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. Scand J Gastroenterol 1989; 24:401-406. doi: 10.3109/00365528909093066
20. Simon TJ, Berlin RG, Gardner AH, Stauffer LA, Gould AL, Getson AJ. Self-Directed Treatment of Intermittent Heartburn: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Evaluation of Antacid and Low Doses of an H(2)-Receptor Antagonist (Famotidine). Am J Ther 1995; 2: 304-313. doi: 10.1097/00045391-199505000-00003
21. Graham DY, Patterson DJ. Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitis. Dig Dis Sci 1983; 28:559-563. doi: 10.1007/BF01308159
22. Tran T, Lowry AM, El-Serag HB. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. Aliment Pharmacol Ther 2007; 25: 143-153. doi: 10.1111/j.1365-2036.2006.03135.x
23. Konturek JW, Beneke M, Koppermann R, Petersen-Braun M, Weingärtner U. The efficacy of hydrotalcite compared with OTC famotidine in the on-demand treatment of gastroesophageal reflux disease: a non-inferiority trial. Med Sci Monit 2007; 13: CR44-CR49.
24. Holtmeier W, Holtmann G, Caspary WF, Weingärtner U. On-demand treatment of acute heartburn with the antacid hydrotalcite compared with famotidine and placebo: randomized double-blind cross-over study. J Clin Gastroenterol 2007; 41: 564-570. doi: 10.1097/MCG.0b013e31802e7efb
25. Xiao YL, Nie YQ, Hou XH, et al. The efficacy, safety and cost-effectiveness of hydrotalcite versus esomeprazole in on-demand therapy of NERD: A multicenter, randomized, open-label study in China. J Dig Dis 2013; 14: 463-468. doi: 10.1111/1751-2980.12069
26. Tytgat GN, Heading RC, Müller-Lissner S, et al. Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting. Aliment Pharmacol Ther 2003; 18: 291-301. doi: 10.1046/j.1365-2036.2003.01679.x
27. Phupong V, Hanprasertpong T. Interventions for heartburn in pregnancy. Cochrane Database Syst Rev 2015; 9: CD011379. doi: 10.1002/14651858.CD011379.pub2

28. Villar J, Belizan JM. Same nutrient, different hypotheses. Disparities in trials of calcium supplementation during pregnancy. Am J Clin Nutr 2000; 71: 1375s–1379s.
29. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomized placebo-controlled trial. Lancet 2002; 359: 1877–1890. doi: 10.1016/S0140-6736(02)08778-0
30. Beaumont H, Bennink RJ, de Jong J, Boeckxstaens GE. The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and patients with GORD. Gut 2010; 59: 441–451. doi: 10.1136/gut.2009.178061
31. Rohof WO, Bennink RJ, Smout AJ, Thomas E, Boeckxstaens GE. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2013; 11: 1585-1591. doi: 10.1016/j.cgh.2013.04.046
32. Lambert JR, Korman MG, Nicholson L, Chan JG. In-vivo anti-reflux and raft properties of alginates. Aliment Pharmacol Ther 1990; 4: 615-622. doi: 10.1111/j.1365-2036.1990.tb00509.x
33. De Ruigh A, Roman S, Chen J, Pandolfino JE, Kahrilas PJ. Gaviscon Double Action Liquid (antacid & alginate) is more effective than antacid in controlling post-prandial oesophageal acid exposure in GERD patients: a double-blind crossover study. Aliment Pharmacol Ther 2014; 40: 531-537. doi: 10.1111/apt.12857
34. Zentilin P, Dulbecco P, Savarino E, et al. An evaluation of the antireflux properties of sodium alginate by means of combined multichannel intraluminal impedance and pH-metry. Aliment Pharmacol Ther 2005; 21: 29-34. doi: 10.1111/j.1365-2036.2004.02298.x
35. Sun J, Yang C, Zhao H, et al. Randomised clinical trial: the clinical efficacy and safety of an alginate-antacid (Gaviscon Double Action) versus placebo, for decreasing upper gastrointestinal symptoms in symptomatic gastroesophageal reflux disease (GERD) in China. Aliment Pharmacol Ther 2015; 42: 845-854. doi: 10.1111/apt.13334
36. Thomas E, Wade A, Crawford G, Jenner B, Levinson N, Wilkinson J. Randomised clinical trial: relief of upper gastrointestinal symptoms by an acid pocket-targeting alginate-antacid (Gaviscon Double Action) - a double-blind, placebo-controlled, pilot study in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2014; 39: 595-602. doi: 10.1111/apt.12640
37. Chatfield S. A comparison of the efficacy of the alginate preparation, Gaviscon Advance, with placebo in the treatment of gastro-oesophageal reflux disease. Curr Med Res Opin 1999; 15: 152-159. doi: 10.1185/03007999909114086
38. McHardy G. A multicentric, randomized clinical trial of Gaviscon in reflux esophagitis. South Med J 1978; 71 Suppl 1: 16-21.
39. Scobie BA. Endoscopically controlled trial of alginate and antacid in reflux oesophagitis. Med J Aust 1976; 1: 627-628.
40. Giannini EG, Zentilin P, Dulbecco P, et al. A comparison between sodium alginate and magaldrate anhydrous in the treatment of patients with gastroesophageal reflux symptoms. Dig Dis Sci 2006; 51: 1904-1909. doi: 10.1007/s10620-006-9284-0
41. Lai IR, Wu MS, Lin JT. Prospective, randomized, and active controlled study of the efficacy of alginic acid and antacid in the treatment of patients with endoscopy-negative reflux disease. World J Gastroenterol 2006; 12: 747-754. doi: 10.3748/wjg.v12.i5.747
42. Chiu CT, Hsu CM, Wang CC, et al. Randomized clinical trial: sodium alginate oral suspension is non-inferior to omeprazole in the treatment of patients with non-erosive gastroesophageal disease. Aliment Pharmacol Ther 2013; 38: 1054-1064. doi: 10.1111/apt.12482
43. Manabe N, Haruma K, Ito M, et al. Efficacy of adding sodium alginate to omeprazole in patients with nonerosive reflux disease: a randomized clinical trial. Dis Esophagus 2012; 25: 373-380. doi: 10.1111/j.1442-2050.2011.01276.x
44. Pouchain D, Bigard MA, Liard F, Childs M, Decaudin A, McVey D. Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. A direct comparative randomised trial. BMC Gastroenterol 2012; 12: 18. doi: 10.1186/1471-230X-12-18
45. Lindow SW, Regnéll P, Sykes J, Little S. An open-label, multicentre study to assess the safety and efficacy of a novel reflux suppressant (Gaviscon Advance) in the treatment of heartburn during pregnancy. Int J Clin Pract 2003; 57: 175-179.
46. Uzan M, Uzan S, Sureau C, Richard-Berthe C. Heartburn and regurgitation in pregnancy. Efficacy and innocuousness of treatment with Gaviscon suspension. Rev Fr Gynecol Obstet 1988; 83: 569-572.
47. Richter JE. Review article: the management of heartburn in pregnancy. Aliment Pharmacol Ther 2005; 22: 749-757. doi: 10.1111/j.1365-2036.2005.02654.x
48. Wang YK, Hsu WH, Wang SS, et al. Current pharmacological management of gastroesophageal reflux disease. Gastroenterol Res Pract 2013; 2013: 983653. doi: 10.1155/2013/983653
49. Gorget C. Sucralfate: development of a new concept of anti-ulcer treatment. Review of its pharmacodynamic properties. Rev Med Interne 1985; 6: 313-319.
50. Candelli M, Carloni E, Armuzzi A, et al. Role of sucralfate in gastrointestinal diseases. Panminerva Med 2000; 42: 55-59.
51. Elsborg L. Oesophageal reflux disease. Diagnosis, pathophysiology and treatment with special reference to the role of sucralfate. Scand J Gastroenterol 1987; 22(Suppl 127): 101-109. doi: 10.3109/00365528709090960
52. Simon B, Ravelli GP, Goffin H. Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1996; 10: 441-446. doi: 10.1111/j.0953-0673.1996.00441.x
53. Herrera JL, Shay SS, McCabe M, Peura DA, Johnson LF. Sucralfate used as adjunctive therapy in patients with severe erosive peptic esophagitis resulting from gastroesophageal reflux. Am J Gastroenterol 1990; 85: 1335-1338.
54. Williams RM, Orlando RC, Bozymski EM, et al. Multicenter trial of sucralfate suspension for the treatment of reflux esophagitis. Am J Med 1987; 83: 61-66. doi: 10.1016/0002-9343(87)90830-8
55. Carling L, Cronstedt J, Engqvist A, et al. Sucralfate versus placebo in reflux esophagitis. A double-blind multicenter study. Scand J Gastroenterol 1988; 23: 1117-1124. doi: 10.3109/00365528809090178
56. Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane Database Syst Rev 2005; (2):CD003245. doi: 10.1002/14651858.CD003245.pub2
57. Vermeijden JR, Tytgat GN, Schotborgh RH, et al. Combination therapy of sucralfate and ranitidine, compared with sucralfate monotherapy, in patients with peptic reflux esophagitis. Scand J Gastroenterol 1992; 27: 81-84. doi: 10.3109/00365529209165421
58. Bremner CG, Marks IN, Segal I, Simjee A. Reflux esophagitis therapy: sucralfate versus ranitidine in a double blind multicenter trial. Am J Med 1991; 91: 119S-122S. doi: 10.1016/0002-9343(91)90462-7
59. Schotborgh RH, Hameeteman W, Dekker W, et al. Combination therapy of sucralfate and cimetidine, compared with sucralfate monotherapy, in patients with peptic reflux esophagitis. Am J Med 1989; 86:77-80. doi: 10.1016/0002-9343(89)90163-0

60. Jørgensen F, Elsborg L. Sucralfate versus cimetidine in the treatment of reflux esophagitis, with special reference to the esophageal motor function. Am J Med 1991; 91: 114S-118S.
61. Tytgat GN, Koelz HR, Vosmaer GD. Sucralfate maintenance therapy in reflux esophagitis. Sucralfate Investigational Working Team. Am J Gastroenterol 1995; 90: 1233-1237.
62. Laitinen S, Ståhlberg M, Kairaluoma MI, et al. Sucralfate and alginate/antacid in reflux esophagitis. Scand J Gastroenterol 1985; 20:229-232. doi: 10.3109/00365528509089662
63. Ranchet G, Gangemi O, Petrone M. Sucralfate in the treatment of gravid pyrosis. G Ital Obstet Ginecol 1990; 12: 1–16.
64. Lansoprazole and sucralfate Drug Interactions - Drugs.com [Internet]. Drugs.com. 2016 [cited 14 October 2016]. [About 1 screen]. Available from: https://www.drugs.com/drug-interactions/lansoprazole-with-sucralfate-1433-0-2118-0.html?professional=1
65. Rekka E, Chrysselis M, Siskou I, Kourounakis A. Synthesis of new azulene derivatives and study of their effect on lipid peroxidation and lipoxygenase activity. Chem Pharm Bull (Tokyo) 2002; 50: 904-907. doi: 10.1248/cpb.50.904
66. Yano S, Horie S, Wakabayashi S, Mochizuki S, Tomiyama A, Watanabe K. Increasing effect of sodium 3-ethyl-7-isopropyl-1-azulenesulfonate 1/3 hydrate (KT1-32), a novel antiulcer agent, on gastric mucosal blood flow in anesthetized. Res Commun Chem Pathol Pharmacol 1990; 70: 253-256.
67. Bergmann JF, Simoneau G, Chantelair G, Caulin C, Segrestaa JM. Use of dimethicone to reduce the fall in gastric potential difference induced by bile salts. Eur J Clin Pharmacol 1989; 36: 379-381. doi: 10.1007/BF00558299
68. Ogilvie AL, Atkinson M. Does dimethicone increase the efficacy of antacids in the treatment of reflux oesophagitis? J R Soc Med 1986; 79: 584-587.
69. Smart HL, Atkinson M. Comparison of a dimethicone/antacid (Asilone gel) with an alginate/antacid (Gaviscon liquid) in the management of reflux oesophagitis. J R Soc Med 1990; 83: 554-556.
70. Leplège A, Mackenzie-Schliacowsky N, Eacute Cosse E, Ruszniewski P. Quality of life scale and impact of a topical treatment on symptoms of gastro-esophageal reflux without severe esophagitis. Gastroenterol Clin Biol 2005; 29: 676-681. doi: GCB-6-7-2005-29-6-7-0399-8320-101019-200514443
71. Ruszniewski P. Etude multicentrique de phase III, randomisé en double aveugle, contrôlé versus placebo, de lefficacité et de la tolérance du gaiazulene associe à la diméticone (Pepsane®) dans le traitement des symptômes de reflux gastro-sophagien non compliqué. Act Med Int Gastroenterologie 2003; 17 (suppl 1): 1-10.
72. Zourabichivili O. Stomalene et pathologie gastro-esophagiene. Med Chi Dig 1986; 15: 217-220.
73. Yoshida N, Kamada K, Tomatsuri N, et al. Management of recurrence of symptoms of gastroesophageal reflux disease: synergistic effect of rebamipide with 15 mg lansoprazole. Dig Dis Sci 2010; 55: 3393-3398. doi: 10.1007/s10620-010-1166-9
74. Katada K, Yoshida N, Isozaki Y, et al. Prevention by rebamipide of acute reflux esophagitis in rats. Dig Dis Sci 2005; 50(Suppl 1): S97-S103. doi: 10.1007/s10620-005-2813-4
75. Adachi K, Furuta K, Miwa H, et al. A study on the efficacy of rebamipide for patients with proton pump inhibitor refractory non-erosive reflux disease. Dig Dis Sci 2012; 57: 1609-1617. doi: 10.1007/s10620-012-2087-6
76. Suzuki T, Matsushima M, Masui A, et al. Irsogladine maleate and rabeprazole in non-erosive reflux disease: A double-blind, placebo-controlled study. World J Gastroenterol 2015; 21: 5023-5031. doi: 10.3748/wjg.v21.i16.5023
77. Volpi N, Schiller J, Stern R, Soltés L. Role, metabolism, chemical modifications and applications of hyaluronan. Curr Med Chem. 2009; 16: 1718-1745. doi: 10.2174/092986709788186138
78. Du Souich P, García AG, Vergés J, Montell E. Immunomodulatory and anti-inflammatory effects of chondroitin sulphate. J Cell Mol Med 2009; 13: 1451-1463. doi: 10.1111/j.1582-4934.2009.00826.x
79. Di Simone MP, Baldi F, Vasina V, Scorrano F, Bacci ML, Ferrieri A, et al. Barrier effect of Esoxx((R)) on esophageal mucosal damage: experimental study on ex-vivo swine model. Clin Exp Gastroenterol 2012; 5: 103-107. doi: 10.2147/CEG.S31404
80. Palmieri B, Merighi A, Corbascio D, Rottigni V, Fistetto G, Esposito A. Fixed combination of hyaluronic acid and chondroitin-sulphate oral formulation in a randomized double blind, placebo controlled study for the treatment of symptoms in patients with non-erosive gastroesophageal reflux. Eur Rev Med Pharmacol Sci 2013; 17: 3272-3278.