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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 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

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.

DOI: http://dx.doi.org/10.15403/jgld.2014.1121.254.dea
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-medicating 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 gaiiazulene 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**

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Level 1 evidence or troublingly inconsistent or inconclusive studies of any level</th>
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<tbody>
<tr>
<td>A</td>
<td>Consistent level 1 studies</td>
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<tr>
<td>B</td>
<td>Consistent level 2 or 3 studies or extrapolations from level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>Level 4 studies or extrapolations from level 2 or 3 studies</td>
</tr>
<tr>
<td>D</td>
<td>Level 5 evidence from the systematic reviews of any level</td>
</tr>
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</table>

“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 gastrroduodenal 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 controlled trials (RCTs) compared antacids (aluminium hydroxide/magnesium carbonate, and magnesium/aluminium 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 crossover 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>
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<th>Experts agreement</th>
<th>Level of evidence</th>
<th>Grade of evidence</th>
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<tbody>
<tr>
<td>Antacids are slightly superior over placebo in treating heartburn</td>
<td>91.6%</td>
<td>2a</td>
<td>Low</td>
<td>B</td>
</tr>
<tr>
<td>Antacids may be used to rapidly relief uncontrolled GERD symptoms</td>
<td>91.6%</td>
<td>2b</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>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</td>
<td>83.3%</td>
<td>2b</td>
<td>Low</td>
<td>B</td>
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<tr>
<td>Antacids (calcium or magnesium-containing antacids) can be used in pregnant women with GERD symptoms</td>
<td>91.6%</td>
<td>4</td>
<td>Very low</td>
<td>C</td>
</tr>
<tr>
<td>In pregnant women, there is no clear difference in the rate of side effects between antacids and placebo</td>
<td>83.3%</td>
<td>4</td>
<td>Very low</td>
<td>C</td>
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</table>

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 571 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<0.0001) [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 = 0.0011) 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].

**Algmates in pregnancy**

Few studies have investigated the safety and efficacy of alginates during 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 to displacement and neutralization of the postprandial gastric acid pocket, rather than preventing reflux.
with the antacid included in the preparation (i.e. magnesium trisilicate or sodium bicarbonate). Therefore, some authors suggested that alginites 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 aluminum 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 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 bedtime) 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

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

GERD: gastroesophageal reflux disease, NERD: Non-erosive reflux disease
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 IV. Recommendations of the Romanian Society of Neurogastroenterology concerning the use of sucralfate in gastroesophageal reflux disease**

<table>
<thead>
<tr>
<th>Statement</th>
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</thead>
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<tr>
<td>Sucralfate is superior over placebo in alleviating GERD symptoms</td>
<td>100%</td>
<td>2a</td>
<td>Low</td>
<td>B</td>
</tr>
<tr>
<td>Sucralfate is as efficient as H2RAs in improving GERD symptoms, and in promoting mucosal healing</td>
<td>91.6%</td>
<td>2b</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Sucralfate can be used as maintenance therapy (after healing of EE with PPIs) in order to prevent relapse of esophagitis</td>
<td>83.3%</td>
<td>2b</td>
<td>Very low</td>
<td>B</td>
</tr>
<tr>
<td>Sucralfate can be used in pregnant women with GERD symptoms</td>
<td>100%</td>
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<td>B</td>
</tr>
</tbody>
</table>

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 relieves GERD symptoms, can induce mucosal healing and can prevent to some extent recurrent esophagitis. However, this mechanism is poorly documented, transforming small gas bubbles in larger ones which are easier to move and eliminate. This mechanism is poorly documented, but several studies showed that dimethicone reduces gas related dyspeptic symptoms, and that dimethicone has a gastroprotective effect [67].

The use of sucralfate is recommended in patients who experience GERD symptoms.

**Note:**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>Low</td>
<td>B</td>
</tr>
<tr>
<td>2b</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>2c</td>
<td>Very low</td>
<td>B</td>
</tr>
</tbody>
</table>

**Use of guaiazulene-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 and anti-oedema action, and increase the blood flow in the mucosa. 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 dimethicone 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].
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 V. Recommendations of the Romanian Society of Neurogastroenterology concerning the use of guaiazulene-dimethicone in gastroesophageal reflux disease

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

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

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


Mucosal protective compounds in GERD


