Symbiosis

www.symbiosisonlinepublishing.com
ISSN Online: 2374-815X

Research Article | Journal of Gastroenterology, Pancreatology & Liver Disorders | Open Access

An Open-Label, Prospective, Single-Center Study of the Combination of Guaiazulene with Dimethicone for Dyspepsia

Yury Marakhouski, Olga Zharskaya*, Galina Karaseva, Elena Adamenko

[1]*Department of Gastroenterology and Nutrition, Belarusian Medical Academy of Postgraduate Education, Minsk, Republic of Belarus*

Received: January 10, 2020; Accepted: June 11, 2020; Published: July 07, 2019

***Corresponding author :** AOlga Zharskaya, PhD, Department of Gastroenterology and Nutrition, Belarusian Medical Academy of Postgraduate Education, 3-3, Brovki Street, Minsk 220013, Republic of Belarus, Tel: +375 29 6 150 085; E-mail: olga_km@mail.ru*

Abstract

Background and Aims: Current therapeutic options for uninvestigated dyspepsia (UD) remain limited and unsatisfactory. Previous studies have shown that the combination of guaiazulene with dimethicone is associated with symptomatic relief and quality of life improvement in patients with gastro esophageal reflux disease. However, only very limited data are available on the use of the guaiazulene-dimethicone combination in UD. Accordingly, we aimed to evaluate whether the guaiazulene-dimethicone combination provides symptomatic relief in patients with UD in Belarus.

Methods: This was a prospective, observational, open-label, single-center, single-arm pilot study. Patients were treated with a combination of 3 g of dimethicone and 4 mg of guaiazulene administered as an oral gel, which was taken as a single-dose sachet thrice daily before meals for 28 days. The effectiveness of the guaiazulene-dimethicone combination was assessed using a simplified adaptation of the Short-Form Leeds Dyspepsia Questionnaire, which was self-completed by all patients at baseline and at Days 14 and 28 of the study. Patients' satisfaction with the guaiazulene-dimethicone combination was also assessed by a nine-item questionnaire completed at Day 28 of the study.

Results: A total of 20 patients with UD were included. Compared to baseline, there was a five- and 27-fold increased odds ratio for improvement in dyspeptic symptoms after 14 and 28 days of treatment, respectively. A 66% relative risk reduction of dyspeptic symptoms was also noted at Day 28. Moreover, an overall patients' treatment satisfaction rate of 70% was recorded. No adverse events were reported during the study, and all patients were compliant with treatment and correctly took the study medications.

Conclusions: The guaiazulene-dimethicone combination was shown to be an effective and well tolerated therapeutic option for patients with UD. This study may be extended with further investigations.

Keywords: Guaiazulene; Dimethicone; Dyspepsia; Patient-reported outcome

Abbreviations: BMI: Body Mass Index; CI: confidence interval; FD: functional dyspepsia; GERD: Gastroesophageal Reflux Disease; H2RAs: Histamine-2 Receptor Antagonists; OD: Odds Ratio; PPIs: Proton Pump Inhibitors; QoL: Quality of Life; RRR: Relative Risk Reduction; SD: standard deviation; SF-LDQ: Short-Form Leeds Dyspepsia Questionnaire; UD: Uninvestigated Dyspepsia.

Introduction

Dyspepsia is a common condition with an extensive differential diagnosis and a heterogeneous pathophysiology [1]. The term "dyspepsia" is used to refer to a spectrum of symptoms localized in the upper abdomen, ranging from pain or discomfort to postprandial fullness, early satiation, bloating, belching, heartburn, nausea, and vomiting [2]. Dyspepsia can be divided into organic and functional dyspepsia (FD). Organic causes of dyspepsia are peptic ulcer, gastro esophageal reflux disease (GERD), gastric or esophageal cancer, pancreatic or biliary tract disorders, intolerance to food or drugs, and other infectious or systemic diseases [2]. However, it is estimated that over 75% of dyspeptic patients have FD with no underlying cause on diagnostic evaluation [3]. According to the recently revised Rome IV criteria, FD is defined as the presence of one or more of the following four symptoms: postprandial fullness, early satiation, epigastric pain or epigastric burning, and no evidence of structural disease (including at upper endoscopy) to explain the symptoms [4]. While patients with these symptoms and a negative diagnostic evaluation likely have FD, according to the Rome IV guidelines, the criteria should be fulfilled for the last three months with symptom onset at least six months before diagnosis [1, 4].

When FD has been confirmed, one of the first treatment measures is exhaustive explanation of the diagnosis and its consequences to the patient [5]. Attention to stress reduction and lowering of anxiety is also important, and dietary advice should be provided (e.g., ingestion of small, regular, low-fat meals and avoidance of foods that precipitate symptoms, if possible) [6]. With regard to medical therapy, multiple drug classes have been trialed to treat FD. These include acid-suppressive drugs such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), *Helicobacter pylori* eradication treatment, prokinetic agents, fundus-relaxing drugs, antidepressants, and phytotherapeutics [2, 5]. However, therapeutic options provide in most cases only

symptomatic benefit and in only a small proportion of patients [3, 7]. Only *Helicobacter pylori* eradication therapy is known to change the natural history of FD [3]. However, after Helicobacter pylori eradication in *Helicobacter pylori*-positive FD, around 10% of patients stay symptom-free in the long term, while in the remaining patients, the symptoms persist or return [5]. Thus, the treatment of FD remains unsatisfactory for many patients [7].

It is important to make a distinction between FD and "uninvestigated dyspepsia" (UD). For a diagnosis of FD to be made, a number of investigations will have been performed and will have been found to be normal, notably upper gastrointestinal endoscopy, upper abdominal ultrasonography, and routine hematology and biochemistry screening blood tests [8]. By contrast, UD refers to patients with either new or possibly recurrent dyspeptic symptoms in whom no investigations have previously been undertaken [8]. The frequency of UD varies considerably in different populations, and such differences may be related to true differences in the frequency of the condition or the criteria used to diagnose UD [9]. The use of endoscopy in the management of UD remains a controversial issue worldwide. Indeed, performing an endoscopy for every dyspeptic patient may not be practical approach, as the high prevalence of the condition will render the required cost and workload unaffordable to any healthcare system [10]. Diagnostic yield and cost-effectiveness will also be low on account of a large portion of UD being functional [10].

Pepsane® is an oral gel containing guaiazulene, a derivative of azulene, at 4 mg in combination with dimethicone (also known as polydimethylsiloxane), a silicon-based organic polymer, at 3 g. Pepsane® is currently marketed in several countries for the symptomatic treatment of functional oesogastroduodenal disorders, including GERD and FD [11]. Previous studies have shown that a dimethicone- and/or a guaiazulene-containing treatment has been effective in the relief of symptoms and was associated with a marked improvement in quality of life (QoL) in patients with GERD [11-15]. However, only very limited data are available on the effectiveness and safety of a dimethicone- and/or a guaiazulene-based therapy in patients with UD. Given the fact that there remains a largely unmet therapeutic need in UD and based on the clinical evidence that a guaiazulene-dimethicone combination may be beneficial in patients with GERD [14, 15], we conducted a prospective, open-label study to evaluate whether guaiazulene-dimethicone provides symptomatic relief in patients with UD.

Methods

Study Design and Study Population

This was a prospective, observational, open-label, single-center, single-arm pilot study conducted in early 2019 in Minsk, Belarus. The study was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and all applicable Belarussian laws and regulations. Local clinical ethics committee approval was obtained to conduct this study. All patients were informed about the nature of the study and signed the informed consent form prior to the conduct of any study-related procedures. Three site visits were carried out during this study: on Day 1 (baseline/visit 1), on Day 14±2 (visit 2), and on Day 28±2 (visit 3).

Consecutive ambulatory patients, who were aged ≥18 years, and who reported bothersome postprandial fullness or early satiation occurring after regular-size meals or epigastric pain or burning at least several times per week during the last six months were eligible for participation in the study [4]. A medical history and physical examination were also completed for each eligible patient to exclude the presence of alarm features or "red flag" symptoms suggestive of upper gastrointestinal malignancy (i.e., unintended weight loss, unexplained iron deficiency anemia, dysphagia, gastrointestinal bleeding, odynophagia, persistent vomiting, and palpable mass or lymphadenopathy) [16].

Exclusion criteria were: (1) pregnancy, breastfeeding, or women of childbearing potential not using effective contraception; (2) any clinically significant medical history or condition that could jeopardize patients' safety and impact the validity of the study results or interfere with the completion of the study according to the protocol (e.g., mental and neurological disorders, cancer, encephalopathy, etc.); (3) organic gastrointestinal or infectious diseases, decompensated diabetes mellitus, acute or chronic pancreatitis, liver or kidney dysfunction, heart or cardiovascular diseases; (4) participation in another clinical study within the last 30 days; (5) use during the last four weeks of medications that interfere with gastrointestinal motility, non-absorbable antibiotics, benzodiazepine receptor antagonists, antidepressants, non-steroidal anti-inflammatory drugs, neuroleptics, nootropics, anxiolytics/sedatives/hypnotics, or immunosuppressive medications; (6) history of hypersensitivity reactions; (7) alcohol consumption in the 48 hours prior to study enrollment; and (8) hemoglobin levels below 80 g/L.

Study Procedures

At baseline, patients underwent screening procedures comprising of assessment of sociodemographic characteristics, medical history (including laboratory test results, prior surgeries, lifestyle habits), and medication history. Patients were also subjected to physical examination and checking of vital signs. After verification of the study inclusion and exclusion criteria, enrolled patients received their first dose of the study medication at the clinic in the presence of the investigator. The study treatment corresponded to a combination of 3 g of dimethicone and 4 mg of guaiazulene administered as an oral gel (Pepsane®, Laboratoires Rosa Phytopharma, France), which was taken as a single-dose sachet three times a day before meals. The total duration of treatment was 28 days. Patients were supplied at baseline with the remaining study medication doses for the period of 28 days. They were also instructed on how to take the study medication; after opening the sachet, the entire content should be taken out of the sachet, squeezed over a tablespoon, and swallowed with a few sips of water. Patient compliance was assessed by the unused

returned drugs and empty packages after 14 and 28 days of treatment.

The effectiveness of the guaiazulene-dimethicone combination was assessed using a simplified adaptation of the Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ), which was self-completed in Russian by all patients at baseline and after 14 and 28 days of treatment [17]. The SF-LDQ assessed five upper gastrointestinal symptoms (heartburn, upper abdominal pain/discomfort, regurgitation, nausea, and belching). Symptoms were first rated for their presence (no or yes). The absence or the presence of a symptom generated a score of 0 or 1 in the analysis, respectively. In the latter case, the patient had to score the symptom on a scale of 0 to 4 for frequency and interference with daily life activities (0–4; 0=not at all, 1=less than once a month, 2=between once a month and once a week, 3=between once a week and once a day, and 4=once a day or more) during the last two months [17]. We used the SF-LDQ to determine the presence, frequency, and severity of dyspeptic symptoms because of its high sensitivity (77.3%) and specificity (73.2%), high test–retest reliability (Pearson's correlation coefficient for test–retest reliability of 0.93), and its good feasibility due to its brevity [17].

Another self-administered questionnaire, which was used to assess patients' perceptions and satisfaction with the guaiazulene-dimethicone combination, was completed on the final study visit after 28 days of treatment. This questionnaire, which was previously validated on a cohort of 2,000 patients with heartburn in Minsk, Belarus, asked the study participants whether they had experienced any gastrointestinal symptoms in the last 14 days and contained eight other items: degree of symptomatic relief after product administration, onset of relief, overall satisfaction, effect on general well-being, confidence in the product's effectiveness, ease of use, convenience, and willingness to continue using the same medication. The first item was rated on a five-category relief scale (no, slight, moderate, significant, and complete relief). The other items were rated on a five-point Likert scale (where 1 was strongly agree, 2 agree, 3 unsure, 4 disagree, and 5 strongly disagree). In the statistical analysis, a positive response (strong agreement or agreement) was marked as 1, and a negative or doubtful response as 0.

In order to enhance self-assessment accuracy, it was planned that every five patients would be managed by one physician-investigator who was responsible for ensuring that all study procedures and questionnaires were fully understood.

Safety was assessed by the analysis of any reports of adverse events, abnormal results of vital signs, and relevant abnormal findings during physical examination that were done at baseline and were repeated during the 14-day and 28-day study visits. All adverse experiences were rated by the study investigator for intensity and relationship to the study product if any.

Outcomes

The primary outcome measure was the change from baseline in the prevalence of UD symptoms after 14 and 28 days of treatment (as assessed by the SF-LDQ). Secondary outcomes included patients' global assessment of the effectiveness of the guaiazulene-dimethicone combination, and patients' willingness to continue treatment after study termination.

Statistical Methods

Based on Isaac and Michael and Hill suggesting that 10 to 30 participants could be included in a pilot study; we expected to enroll at least 10 patients [18, 19].

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population at baseline. In general, findings were reported for categorical variables as frequencies and percentages, while mean, standard deviation (SD), median, and interquartile range was used to describe continuous variables. For comparison of clinical symptoms before and after treatment, Wilcoxon rank-sum test and McNemar's test were applied. Fisher's exact test and Cochran–Mantel–Haenszel test were also applied to analyze categorical data.

We used canonical correlation analysis to examine the association between the occurrence of FD symptoms and satisfaction with the guaiazulene-dimethicone combination. The Kruskal-Wallis one-way analysis of variance by ranks was also performed to evaluate the investigators' impact on the filling out process of the SF-LDQ by the study participants and to adjust for any potential investigator bias.

All statistical tests were two-sided and were performed at a 0.05 significance level. Statistical analyses were conducted using Statistica (version 6.0, Dell, TX, USA), WinPepi (version 4.0, Brixton Health, Wales, UK), and NCSS (2004, NCSS LLC, UT, USA).

Results

Patient Characteristics

A total of 20 patients (10 men and 10 women) with UD who fulfilled the eligibility criteria were included in the study. All enrolled patients successfully completed the study. Patients' baseline characteristics are summarized in Table 1. The mean age of the study population was 43.8 (range 24 – 68) years, and only six patients (30%) were overweight (according to the World Health Organization classification) with a body mass index (BMI) ranging from 25.5 to 30.5 kg/m^2. The other 14 patients had a BMI ranging from 18.5 to 24.0 kg/m^2. Most study participants were non-smokers (15/20, 75%). Similarly, 14 patients (70%) did not consume any alcohol at all, while six patients reported occasional alcohol consumption. Except for UD, none of the subjects had a relevant medical history at the time of enrollment. There were no clinically significant abnormalities found in the physical examination and in the vital sign assessment.

At baseline, all 20 patients (100%) reported having at least three dyspeptic symptoms. Seven (35%) and five (25%) patients reported having four and five dyspeptic symptoms, respectively. Abdominal pain/discomfort was the most commonly reported symptom (in 100% of study subjects), followed by belching

Table 1: Baseline characteristics of the 20 patients with uninvestigated dyspepsia	
Baseline Characteristic	Study Population (N=20)
Mean ± SD age (median; IQR) – years	43.8 ± 13.8 (45.5; 32.0 – 57.0)
Gender (male to female ratio)	1:1
Highest educational attainment – n (%)	
Primary	0(0)
Secondary	6(30)
Tertiary	14(70)
Marital status – n (%)	
Unmarried/separated/divorced	2(10)
Married	18(90)
Widowed	0(0)
Mean ± SD weight (median; IQR) – kg	69.8 ± 11.3 (70.0; 63.0 – 74.5)
Mean ± SD BMI (median; IQR) – kg/m^2	23.5 ± 3.1 (22.8; 21.3 – 25.5)
Mean ± SD SBP (median; IQR) – mmHg	116.0 ± 7.0 (116.0; 110.0 – 120.0)
Mean ± SD DBP (median; IQR) – mmHg	72.0 ± 8.0 (70.0; 70.0 – 78.0)
Dyspeptic symptom – n (%)	
Abdominal pain/discomfort	20(100)
Belching	18(90)
Heartburn	16(80)
Nausea	13(65)
Regurgitation (with acid content)	10(50)
Percentages are calculated as n/N. BMI: Body Mass Index; DBP: Diastolic Blood Pressure; IQR: Interquartile Range; SBP: Systolic Blood Pressure; SD: Standard Deviation.	

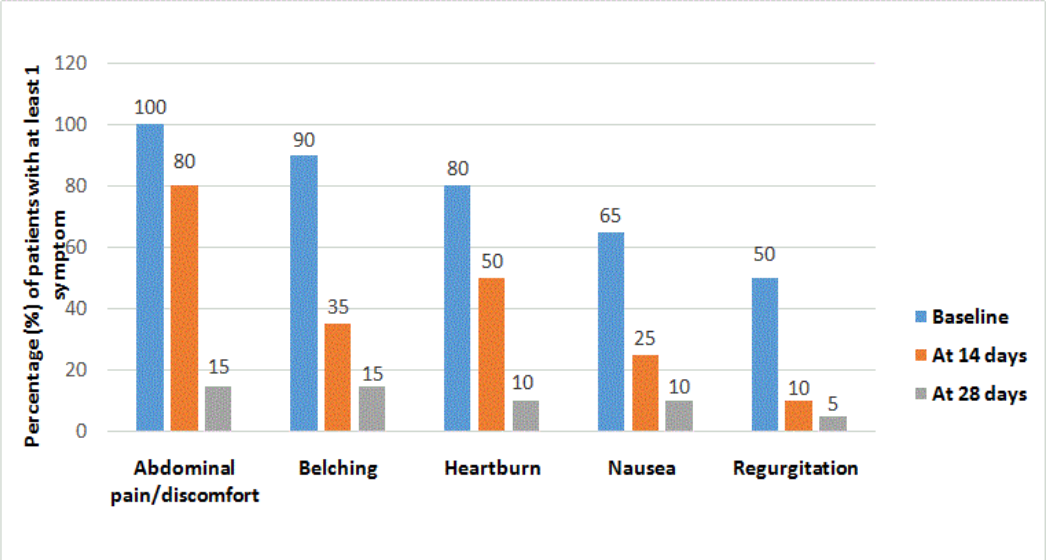

Figure 1: Frequency of dyspepsia symptoms over the 28-day treatment period

(90%) and heartburn (80%).

Symptom Improvement

As illustrated in Figure 1, data from the SF-LDQ indicated that the guaiazulene-dimethicone combination resulted in a significant improvement in dyspeptic symptoms in the study population after 14 and 28 days of treatment ($p<0.05$ compared to baseline for both time points). Indeed, after 14 days of treatment, the guaiazulene-dimethicone combination was significantly associated with five-fold increased odds for improvement in dyspeptic symptoms (odds ratio [OR] 5.02; 95% confidence interval [CI] 1.28 – 19.65; $p=0.017$). Moreover, compared to baseline, a 37% relative risk reduction (RRR) of dyspeptic symptoms was found at the 14-day study visit (95% CI 7.83% – 66.17%).

Further symptomatic improvement was observed after 28 days of treatment. Compared to baseline, there was a 27-fold increased likelihood of improvement in dyspeptic symptoms (OR 27.09; 95% CI 7.63 – 96.17; $p<0.001$). In addition, a 66% RRR of dyspeptic symptoms was noted at the 28-day study visit (95% CI 48.19% – 83.81%).

Consistently, at the 28-day study visit, a significant improvement in all individual dyspepsia symptoms was observed compared with the 14-day visit (OR 5.39; 95% CI 1.40 – 20.82; $p=0.017$), with a RRR of 29% (95% CI 5.31% – 52.69%). Furthermore, compared to baseline where there were no asymptomatic patients, two patients (10%) were completely asymptomatic after 14 days of therapy versus 13 patients (65%) after 28 days.

None of the patients reported any worsening of the symptoms during the 28-day treatment period.

Treatment Satisfaction

The treatment satisfaction questionnaire was completed by all 20 patients (100%) at the 28-day study visit. Overall, 75% of patients experienced a significant or a complete symptomatic relief after administration of the guaiazulene-dimethicone combination. Similarly, 75% of patients were quite or highly confident in the study medication's effectiveness. Moreover, 80% of the patients expressed satisfaction with the onset of action of the guaiazulene-dimethicone combination and its effect on general well-being (i.e., feeling healthier and happier). All patients (100%) agreed that the study medication was associated with ease of use and convenience of administration. Patients very or quite motivated to continue using the guaiazulene-dimethicone combination represented 70%. These positive judgments translated into an overall patient satisfaction rate of 70% (95% CI 45.7% – 88.1%).

A canonical correlation coefficient of –0.8 was obtained, which means that greater patient satisfaction was associated with a reduction in the likelihood of occurrence of dyspeptic symptoms after 14 and 28 days of treatment.

None of the patients reported adverse events during the course of the study, and all 20 patients were compliant with treatment and correctly took the study medications.

Discussion

The results of the present prospective, open-label, single-arm study support the effectiveness of guaiazulene-dimethicone in relieving the symptoms associated with UD. Moreover, the guaiazulene-dimethicone combination was associated in our study with high patient-reported satisfaction and compliance, with no reported notable adverse events.

Dyspepsia is a clinical condition of considerable magnitude due to its high and rising prevalence, and the chronic and recurrent nature of symptoms, which management is a challenge for gastroenterologists [20]. A recent cross-sectional, population-based study, conducted among 5,931 adults from the United States, Canada, and Great Britain, found that approximately 10% of the adult population fulfilled symptom-based criteria for Rome IV FD which was associated with significant health impairment [21]. Regarding the subtype distribution, 61% of study participants with FD suffered from postprandial distress syndrome, 18% from epigastric pain syndrome, and 21% from the overlapping variant with both syndromes [21]. Similarly, a meta-analysis of 100 population-based studies including 312,415 subjects found a pooled UD prevalence of 20.8% [22]. However, the prevalence of UD varied among countries (from 1.8% in Canada to 57.0% in Japan), and according to the criteria used to define its presence. The prevalence of UD was highest when a broad definition of dyspepsia was used (29.5%), and lowest when the Rome III criteria were used (7.6%) [22].

The therapeutic options for UD in general and for FD in particular are limited with conflicting results in terms of efficacy [20]. Indeed, it has been shown that the utility of *Helicobacter pylori* eradication for the treatment of FD in *Helicobacter pylori*-positive patients is modest (therapeutic gain of 6% to 14%). The effectiveness of PPIs in the treatment of FD also appears to be modest with a therapeutic gain of approximately 7% to 10%. Similarly, even though patients with FD were more likely to respond to H2RAs than placebo in clinical trials, the effect of these drugs is likely to be small. Finally, although prokinetic agents are conceptually appealing given their potential to improve gastric emptying and are commonly used throughout the world, the results in patients with FD are underwhelming [7]. Thus, new therapeutic possibilities remain largely needed.

The encouraging findings of our study are supported by previous preclinical and phase I studies which showed that both guaiazulene and dimethicone have gastro protective effects [23-27]. In a placebo-controlled, randomized trial by Bergmann et al. carried out in 10 healthy volunteers after sodium taurodeoxycholate intake, oral administration of dimethicone 2.25 g reduced the bile salt-induced lowering of the transgastric potential difference [23]. Hence, this study suggested that dimethicone can prevent the formation of the gastric lesions induced by bile salts [23]. In an ex vivo study by Yano et al. conducted in anesthetized male Wistar rats, the azulene derivative KT1-32 produced a dose-dependent increase in gastric mucosal blood flow, and it was suggested that the increasing effect of KT1-32 on gastric mucosal blood flow

contributes to its gastroprotective activity through strengthening mucosal defensive mechanisms [24]. In an in vitro study by Rekka et al., it was reported that guaiazulene and chamazulene, another azulene derivative, have antioxidant and anti-inflammatory activities [25]. The antioxidant activity of these compounds was found to increase with lipophilicity, and this increase in lipophilicity facilitates their access, retention, as well as interaction with biological membranes [25]. Since dimethicone is a lipophilic substance, its combination with guaiazulene enhances the latter's antioxidant effect and its interaction with membrane lipids. More recently, the anti-ulcer activity of guaiazulene derivatives and omeprazole (used as a positive control) was tested through an ethanol-induced gastric ulcer mouse model [26]. All of the guaiazulene derivatives demonstrated anti-ulcer activity, and most of them exhibited better anti-ulcer activity than omeprazole. The authors speculated that the gastro protective effect of guaiazulene derivatives could be attributed to surface coverage and multifunctional group synergistic mechanisms [27].

Dyspeptic symptoms can significantly impair patients' QoL [3]. In a population-based study from Northern Sweden in 1,000 patients, it was found that FD significantly impacts all main domains describing physical, mental and social aspects of health-related QoL [28]. Patients with FD have reduced health-related QoL because their symptoms, particularly abdominal pain, cause emotional distress, a reduced intake of foods and drinks, and impaired vitality [29]. Moreover, FD produces heavy economic burdens by demanding extensive medical care and diagnostic procedures and also by causing an inability to work or participate in educational activities [30].

In the present study, the guaiazulene-dimethicone combination gel was associated with an improved QoL, since most patients reported that the study medication administration had positive effects on both their symptoms and their general well-being. This is in line with the findings of previous randomized controlled trials evaluating guaiazulene and/or dimethicone in patients with GERD [12-14]. In a double-blind trial by Ogilvie and Atkinson conducted in 38 patients with symptomatic GERD, an endoscopic evidence of esophagitis, and a positive acid perfusion test, patients were randomized to receive for eight weeks either an antacid-dimethicone oral gel or an identically formulated gel containing the antacid alone [12]. Both treatments similarly reduced pain and symptom scores at Weeks 4 and 8 of the study. However, there was a trend for the antacid-dimethicone gel to better improve esophageal inflammation [12]. In another eight-week, double-blind trial comparing the efficacy of dimethicone-antacid versus alginate-antacid in 53 patients with symptomatic GERD associated with endoscopic evidence of esophagitis, dimethicone-antacid but not alginate-antacid significantly improved the grade of endoscopic esophagitis and esophageal ulceration ($p<0.02$ compared to baseline), although the proportion of patients with a normal endoscopic esophageal appearance at trial conclusion did not differ significantly between the two groups [13]. According to the authors, this may be a real finding or related to the small number of included patients inducing a type II error [13]. In a more recent double-blind, randomized, controlled trial of guaiazulene in combination with dimethicone versus placebo administered as an oral gel for four weeks in 233 patients with GERD symptoms, the primary endpoint of the study, which was a ≥50% reduction in the global symptomatic score at 14 days, was achieved in 54.1% of patients in the guaiazulene-dimethicone group versus 41.1% in the placebo group [14]. After four weeks of treatment, QoL scores in the guaiazulene-dimethicone group were similar with those observed in the general population, but remained significantly lower in the placebo group [14].

Despite the available evidence on the effectiveness of guaiazulene-dimethicone in patients with GERD, there is limited data regarding the use of these two compounds in UD. To our knowledge, the present study is the first in Belarus to evaluate the use of guaiazulene-dimethicone in UD. Our study was based on patient self-assessments and selected patient-reported outcomes. It is well recognized that the outcome of dyspepsia management is dependent on patients' perception of their well-being in relevant physical, emotional, and social domains [31]. As such, clinicians and investigators must rely on patients' assessments of their symptoms for managing UD and evaluating treatment effectiveness [32].

The present study had some limitations. The small patient population and the absence of a control arm do not allow us to draw any definite conclusion about the efficacy of the guaiazulene-dimethicone combination gel. Despite these limitations, our study had several strengths, including the use of reliable, valid and responsive self-completed tools for the assessment of symptomatic improvement and treatment satisfaction, and the absence of missing data.

In conclusion, our study showed that the combination of 3 g of dimethicone and 4 mg of guaiazulene, administered as an oral gel thrice daily before meals, provided symptomatic relief in patients with UD, and was associated with good compliance and high patient-reported satisfaction. The combination was also found to be well tolerated with a good safety profile. Making optimal use of guaiazulene-dimethicone might delay symptom relapse and further improve the QoL of patients with dyspepsia. However, this remains to be proven by larger studies with objective assessments and long-term follow-up.

Acknowledgments

The authors would like to thank Thomas Rohban, MD and Magalie El Hajj, PharmD (Partner 4 Health, France) for providing medical writing support in accordance with Good Publication Practice (GPP3) guidelines.

Conflict of Interest

The authors have no conflicts of interest to declare.

Ethical Approval

All study participants provided written informed consent. The study protocol was approved by the Ethics Committee of the 10th City Clinical Hospital, Minsk, Belarus.

Author Contributions

Y.M. conceived the study. Y. M. and O.Z. designed the study. Y.M., O.Z., G.K., and E.A. participated in the acquisition, analysis, and interpretation of data. O.Z., G.K., and E.A. contributed to the writing of the manuscript. All authors critically reviewed and approved the final draft of the manuscript.

References

1. Enck P, Azpiroz F, Boeckxstaens G, Elsenbruch S, Feinle-Bisset C, Holtmann G, et al. Functional dyspepsia. Nat Rev Dis Primers. 2017;3:17081. doi: 10.1038/nrdp.2017.81.
2. Oustamanolakis P, Tack J. Dyspepsia: organic versus functional. J Clin Gastroenterol. 2012 Mar;46(3):175-190. doi: 10.1097/MCG.0b013e318241b335.
3. Talley NJ. Functional Dyspepsia: Advances in Diagnosis and Therapy. Gut Liver. 2017;11(3):349-357. doi: 10.5009/gnl16055.
4. Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal Disorders. Gastroenterology. 2016;150(6):1380-1392. doi: 10.1053/j.gastro.2016.02.011.
5. Madisch A, Andresen V, Enck P, Labenz J, Frieling T, Schemann M. The Diagnosis and Treatment of Functional Dyspepsia. Dtsch Arztebl Int. 2018;115(13):222-232. doi: 10.3238/arztebl.2018.0222.
6. Talley NJ, Ford AC. Functional Dyspepsia. N Engl J Med. 2015;373(19):1853-1863. doi: 10.1056/NEJMra1501505.
7. Lacy BE, Talley NJ, Locke GR 3rd, Bouras EP, DiBaise JK, El-Serag HB, et al. Review article: current treatment options and management of functional dyspepsia. Aliment Pharmacol Ther. 2012;36(1):3-15. doi: 10.1111/j.1365-2036.2012.05128.x.
8. Jones RH. Approaches to uninvestigated dyspepsia. Gut. 2002;50 Suppl 4:iv42-6. doi: 10.1136/gut.50.suppl_4.iv42.
9. Ghoshal UC, Singh R, Chang FY, Hou X, Wong BC, Kachintorn U. Functional Dyspepsia Consensus Team of the Asian Neurogastroenterology and Motility Association and the Asian Pacific Association of Gastroenterology. Epidemiology of uninvestigated and functional dyspepsia in Asia: facts and fiction. J Neurogastroenterol Motil. 2011;17(3):235-244. doi: 10.5056/jnm.2011.17.3.235.
10. Hsu YC, Yang TH, Liou JM, Hsu WL, Lin HJ, Wu HT, et al. Can clinical features stratify use of endoscopy for dyspeptic patients with high background prevalence of upper gastrointestinal cancer? Dig Liver Dis. 2012;44(3):218-223. doi: 10.1016/j.dld.2011.10.012.
11. Surdea-Blaga T, Băncilă I, Dobru D, Drug V, Frăţilă O, Goldiş A, et al. Mucosal Protective Compounds in the Treatment of Gastroesophageal Reflux Disease. A Position Paper Based on Evidence of the Romanian Society of Neurogastroenterology. J Gastrointestin Liver Dis. 2016;25(4):537-546. doi: 10.15403/jgld.2014.1121.254.dea.
12. Ogilvie AL, Atkinson M. Does dimethicone increase the efficacy of antacids in the treatment of reflux oesophagitis? J R Soc Med. 1986;79(10):584-587. doi: 10.1177/014107688607901009.
13. 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(9):554-556.
14. 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(6-7):676-681. doi: 10.1016/s0399-8320(05)82156-6.
15. Loranskaia ID, Rakitskaia LG, Mamedova LD, Vishnevskaia VV, Malakhova EV. Pepsane-R administration in the treatment of gastroesophageal reflux disease. Eksp Klin Gastroenterol. 2008;(4):78-82.
16. Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. Gastroenterology. 2005;129(5):1756-1780. doi: 10.1053/j.gastro.2005.09.020.
17. Fraser A, Delaney BC, Ford AC, Qume M, Moayyedi P. The Short-Form Leeds Dyspepsia Questionnaire validation study. Aliment Pharmacol Ther. 2007;25(4):477-486. doi: 10.1111/j.1365-2036.2006.03233.x.
18. Isaac S, Michael WB. Handbook in research and evaluation. San Diego, CA: Educational and Industrial Testing Services; 1995.
19. Hill R. What sample size is "enough" in internet survey research? Interpersonal Computing and Technology: An Electronic Journal for the 21st Century. 1998;6(3-4). Available from: http://cadcommunity.pbworks.com/f/what%20sample%20size.pdf. [Accessed 2020].
20. Majeed M, Majeed S, Nagabhushanam K, Arumugam S, Pande A, Paschapur M, et al. Evaluation of the Safety and Efficacy of a Multienzyme Complex in Patients with Functional Dyspepsia: A Randomized, Double-Blind, Placebo-Controlled Study. J Med Food. 2018;21(11):1120-1128. doi: 10.1089/jmf.2017.4172.
21. Aziz I, Palsson OS, Törnblom H, Sperber AD, Whitehead WE, Simrén M. Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study. Lancet Gastroenterol Hepatol. 2018;3(4):252-262. doi: 10.1016/S2468-1253(18)30003-7.
22. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. Gut. 2015;64(7):1049-1057. doi: 10.1136/gutjnl-2014-307843.
23. 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(4):379-381. doi: 10.1007/bf00558299.
24. 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(2):253-256.
25. 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(7):904-907. doi: 10.1248/cpb.50.904.
26. Franchi E, Ingrosso G, Marchetti F, Pinzino C. Guaiazulene-based phenolic radical scavengers: synthesis, properties, and EPR studies of their reaction with oxygen-centred radicals. Tetrahedron. 2003;59(27):5003-5018. doi: 10.1016/S0040-4020(03)00737-3.
27. Cao T, Li Y, Yang Z, Yuan M, Li Y, Yang H, et al. Synthesis and Biological Evaluation of 3, 8-dimethyl-5-isopropylazulene Derivatives as Anti-

gastric Ulcer Agent. Chem Biol Drug Des. 2016;88(2):264-271. doi: 10.1111/cbdd.12753.

28. Aro P, Talley NJ, Agréus L, Johansson SE, Bolling-Sternevald E, Storskrubb T, et al. Functional dyspepsia impairs quality of life in the adult population. Aliment Pharmacol Ther. 2011;33(11):1215-1224. doi: 10.1111/j.1365-2036.2011.04640.x.
29. Halling K, Kulich K, Carlsson J, Wiklund I. An international comparison of the burden of illness in patients with dyspepsia. Dig Dis. 2008;26(3):264-273. doi: 10.1159/000128576.
30. Brun R, Kuo B. Functional dyspepsia. Therap Adv Gastroenterol. 2010;3(3):145-164. doi: 10.1177/1756283X10362639.
31. Mahadeva S, Wee HL, Goh KL, Thumboo J. Quality of life in South East Asian patients who consult for dyspepsia: validation of the short form Nepean Dyspepsia Index. Health Qual Life Outcomes. 2009;7:45. doi: 10.1186/1477-7525-7-45. doi: 10.1186/1477-7525-7-45.
32. Leidy NK, Farup C, Rentz AM, Ganoczy D, Koch KL. Patient-based assessment in dyspepsia: development and validation of Dyspepsia Symptom Severity Index (DSSI). Dig Dis Sci. 2000;45(6):1172-1179. doi: 10.1023/a:1005558204440.