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Research Article

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Rebamipide and its Use in Clinical Practice (Literature Review, Meta-Analysis and Our Experience), Part I. Preventive and Therapeutic Effect of Rebamipide in NSAID-Induced Gastroenteropathies

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ABSTRACT

Introduction: In clinical practice, the prevalence of NSAID-induced damage to the esophagus, stomach, and intestines is of great importance, as it is dangerous for the occurrence of significant bleeding, sometimes leads to death, requires huge material costs, significantly disrupts the quality of life of patients. Gastroenteroprotector rebampide has been widely used in the treatment of a wide range of diseases of the gastrointestinal tract and its special position in the prevention and treatment of NSAID-induced damage to the gastrointestinal tract. However, there are some questions to the evidence base.

Aim: Our work was to analyze the available data on the use of rebamipide in the prevention and treatment of NSAID-induced esophagogastroenteropathy from the perspective of evidence-based medicine.

Methods: A search through various databases for randomized controlled studies on the use of rebamipide as monotherapy or in combination with an PPI or hystamine H2-receptor blocker revealed 24 studies. A meta-analysis of the use of rebamipide for the prevention and treatment of NSAID-induced esophagogastroenteropathy was conducted. In addition, a review and analysis of the available meta-analyses of the use of rebamipide and the assessment of its effectiveness in comparison with other drugs in terms of efficacy and safety were conducted.

Conclusions: our meta-analysis proved the efficacy and safety of rebamipide in the prevention and treatment of gastrointestinal injuries caused by the use of NSAIDs, which was also confirmed by previous meta-analyses and certain recommendations and consensus of various communities of specialists dealing with this problem.

Keywords: Rebamipide, NSAIDs, Gastroenteropathy, Prevention, Treatment.

Introduction

The trigger for writing this work was the great interest in the drug rebamipide, the possibility of using the drug in a variety of diseases of the gastrointestinal tract (GIT), as well as in diseases of other organs and systems. This widespread use of rebamipide is explained by its pleiotropic effect. It is known that the pleiotropic effect of any drug is a beneficial effect on various pathogenetic mechanisms of disease development, except for the main one against which this drug was created (See Figure 1 and 2) The relevance and enormous importance of Rebamipide in the treatment of diseases of various body systems, and the presence of some controversial issues prompted us to thoroughly analyze all available data on rebamipide (Pubmed/Medline, Cochrane Library, Embase, Scopus, Google Scholar, Web of Science, Russian Science Citation Index – e-library.ru, Russian Gastroenterological Association, AGA, ACG journals, and many others). Each topic of the drug's use was evaluated from the point of view of evidence-based medicine.

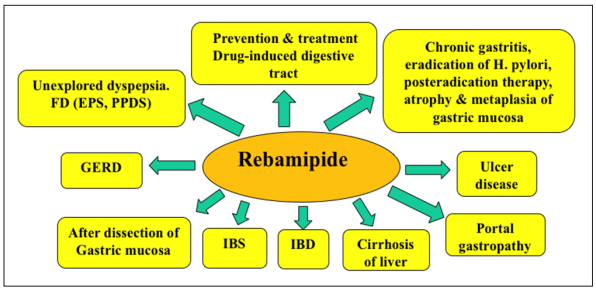

Figure-1: Pleiotropic Effects of Rebamipide on the Gastrointestinal Tract.
FD – Functional Dyspepsia, EPS – Epigastric Pain Syndrome,

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PPDS – Postprandial Distress Syndrome.

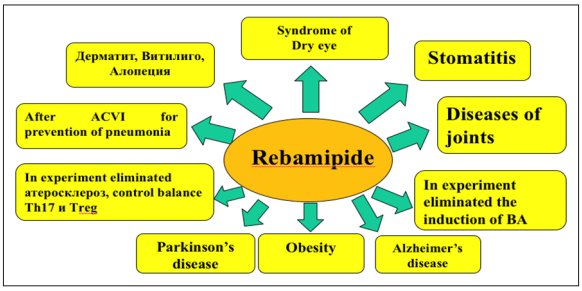

Figure-2: Pleiotropic Effects of Rebamipide Outside the GIT. ACVA – Acute Cerebrovascular Accident, GIT – Gastrointestinal Tract.

Rebamipide, a quinolinone derivative, was synthesized and developed by the Japanese pharmaceutical company Otsuka, and was initially introduced to the pharmaceutical market as Mucosta® for the treatment of gastric ulcers in 1990, and for the treatment of gastritis in 1994. In Russia, a high-quality analogue of Rebagit (rebamipide PRO.MED.CS Praga) has been used since 1997. The drug is available in tablet form and as eye drops. In addition to Rebagit, 8 Russian and 1 Indian analogues of rebamipide there are on the pharmaceutical market of the Russian Federation. The first experimental studies on the quinolinone derivative to investigate the possibility of preventing the development of ulcers in rats exposed to various ulcerogenic substances were published in 1985 [1]. Subsequently, there was a growing interest in the properties of rebamipide. Over the past 20 years, since 2005, the National Library of Medicine (PubMed) has published 20 times more articles on rebamipide than in the previous 20 years, and in 2025, the tenth part of all previously published works. Significant works on the use of rebagit in clinical practice have been published by our leading Russian gastroenterologists V.T. Ivashkin, N.V. Bakulina, I.G. Bakulin, I.V. Mayev, V.I. Simanenkov, and Yu.P. Uspensky.

Table 1: Characteristics of included studies.

Author	Side	Population, mean age, M/F	NSAIDs	Investigational drug	Comparison
Naito Y, et al. 1998 [20]	Japan	20 healthy, 21,5 against 22.0 years; All man. 10 – Reb + Ind. 10 – Pl.+ Ind.	Indomethacin 25 mg t.i.d	Rebamipide 100 mg t.i.d	Placebo
Kim H-K, et al. 2007 [21]	Korea	20 healthy, 26.5 years; 9 man/11 woman.	Ibuprofen 600 mg t.i.d	Rebamipide 100 mg t.i.d	Placebo
Kawai T, et al. 2009 [22]	Japan	20 healthy, 24 years; 16 man/4 woman.	Aspirin 100 mg OD	Rebamipide 100 mg t.i.d	Placebo
Ono S, et al. 2009 [23]	Japan	20 healthy, 24 years; 15 man/5 woman.	Aspirin 81 mg OD	Rebamipide 100 mg t.i.d	Placebo
Nishida U, et al. 2011 [24]	Japan	10 healthy, 29 years; All man.	Aspirin 100 мг mg OD	Rebamipide 100 mg t.i.d	Placebo
Hasegawa M, et al. 2013 [25]	Japan	65 patients with RA - 24, OA – 25 and low back pain 20; 67 years; 16 man/49 woman.	Celecoxib 100 mg b.i.d	Rebamipide 100 mg t.i.d	Placebo
Kurokawa S, et al. 2014 [26]	Japan	61 patient with NSAID-induced enteropathy, older 65 years 86.7%/ 77.4%. Man 50% against 48.4%.	Aspirin 100 мг OD or NSAID	Rebamipide 100 mg t.i.d	Placebo
Tozawa K, et al. 2014 [27]	Japan	32 healthy - All man, 29.8 years in 1-st group (Pl + LDA), 28.1 years in 2-nd group (Reb + LDA), 29.1years in third group (Pl + LDA + Clopidr), 29.7 years in 4-th group (Reb + LDA + Clopidr).	Aspirin 100 mg OD или Aspirin 100 mg OD + Clopidrogel 75 mg OD	Rebamipide 100 mg t.i.d	Placebo
Watanabe T, et al. 2015 [28]	Japan	38 patients with c CerVD или CarVD, 74.5 years. Man – 25, Woman – 13.	Aspirin 100 mg OD	Rebamipide 100 mg t.i.d	Placebo
Gagliano-Juca T, et al. 2016 [29]	Brazil	24 healthy, 26.5 years; Man – 12; Woman – 13.	Naproxen 550 mg 2 р/д	Rebamipide 100 mg t.i.d	Placebo
Tkach S., et al., 2017 [30]	Ukraine	118 patients with OA (n=94) and RA (n=24). 45 years.	Diclofenac 100 mg OD.	Rebamipide 100 mg t.i.d	Om 20 mg OD
Pittayanon R, et al, 2019 [31]	Thailand	95 patients, randomized 83. 42 patients in group of Rebamipide, 61.4 years. 27 man, 15 woman. 41 patient in group of Placebo, 59.5 years. 33 man, 8 woman.	Aspirin 81 mg + Clopidrogel. Aspirin 81 mg + silostazol 200 mg. Aspirin 81 mg + tisagrelor 90 mg. Aspirin 300 mg + Clopidrogel 75 mg	Rebamipide 100 mg t.i.d	Placebo

Park S-H, et al. 2007 [35]	Korea, China, Thailand	410 patients, 47 years; NSAID + Rebamipide – 207. NSAID + Misoprostol – 203. Man– 121, Woman – 289.	NSAID (diclofenac, aceclofenac, naproxen, sulindac, ibuprofen, fenoprofen)	Rebamipide 100 mg t.i.d	Mizoprostol 200 μg t.i.d
Kim J, et al. 2014 [36]	Korea	479 patients, 55.8 years; Man - 86; Woman – 393. NSAID + Rebamipide – 242. NSAID + Misoprostol – 237.	NSAID (aceclofenac 100 mg OD or Meloxicam 7.5 mg OD or Nabumeton 500 mg OD)	Rebamipide 100 mg t.i.d	Mizoprostol 200 μg t.i.d
Niwa Y, et al. 2011 [11]	Japan	10 healthy, Placebo (n=10) or Rebamipide (n=10).	Diclofenac 75 mg OD	Rebamipide 100 mg t.i.d + Omeprazole 20 mg OD.	Placebo + Omeprazole 20 mg OD
Mizukami K, et al. 2011 [12]	Japan	11 healthy, 30 years. All man.	Aspirin 100 mg OD	Rebamipide 100 mg t.i.d + Omeprazole 20 mg OD.	Placebo + Omeprazole 20 mg OD.
Mizukami K, et al. 2011 [13]	Japan	12 healthy, All man.	Aspirin 100 mg OD	Rebamipide 100 mg t.i.d +Omeprazole 20 mg OD	Placebo + Omeprazole 20 mg OD
Fujimori S, et al. 2011 [14]	Japan	72 healthy, NSAID + Om + Pl – 38; NSAID + Om + Rebamipide – 34.	Diclofenac 75 mg OD	Rebamipide 100 mg t.i.d +Omeprazole 20 mg OD	Pl + Om 20 mg OD
Ito Y, et al, et al. 2013 [37]	Japan	10 healthy, 34 years. Man -7, Woman – 3. Diclofenac + Omeprazole + Placebo or Д + Ом + Реб.	Diclofenac 75 mg OD	Rebamipide 100 mg t.i.d +Omeprazole 20 mg OD	Pl + Om 20 mg OD
Mbarki M, et al. 2017 [38]	Ukraine	102 patients with CVD, 64.7 years, 55 man and 47 woman. n= 37 (group ASA), n=33 (group ASA + PPI), n=32 (group ASA + PPI + Rebamipide).	ASA	ASA + Pant + Reb	ASA + Pantoprazole
Ota K, et al. 2016 [39]	Japan	45 healthy, 35.8 years, gender distribution is not specified.	Aspirin 100 mgr OD	Rebamipide 100 mg t.i.d Rebamipide 300 mg t.i.d	Omeprazole 10 mg OD
Oh DJ, et al. 2022 [40]	Korea, Chaina	33 patients with c RA, OA, AC, 55.8 years; Man – 14, Woman – 19.	Meloxicam 15 mg t.i.d	Rebamipide 100 mg t.i.d	Lansoprazole 15 mg OD
Yamamoto T, et al. 2010 [41]	Japan	530 patients with c CHD (66%), CerVD (30%), systemic atherosclerosis (8%) of these 25 patients with GB, 70.3 years (man – 14, woman 11) and 192 with gastric mucosal injuries, 69.2 years. (man 295, woman 235).	Aspirin 100 mg OD	PPI + Rebamipide BH2RH	PPI+MD BH2RH + MD
Jia R-J, 2022, et al. [42]	Chaina	360 patient with double antiplatelet therapy, 70.2 years, man 284, woman – 76.	Aspirin 100 мг 1 р/д + Clopidrogel 75 mg OD	Rabeprazole 20 mg OD or Rebamipide 100 mg t.i.d	Rab + Reb
Naito Y, et al. 2008 [43]	Japan	12 healthy, 21.9 years; all man.	Indomethacin 25 mg t.i.d	Rebamipide 100 mg t.i.d	Famotidin 10 mg b.i.d
Yamao J-I, et al. 2007 [44]	Japan	112 patients with NSAID-associated gastropathy. Reb – 55, Fam -57, 54.7 years in group Fam, 57.3 in group Reb.	NSAID	Rebamipide 100 mg t.i.d	Famotidin 20 mg b.i.d

NSAID – nonsteroid antiinflammatory drugs, Reb – rebamipide, Ind – indomethacin, OD – once day, RA – rheumatoid arthritis, OA – osteoarthritis, CarVD – cardiovascular disease, CerVD – cerebrovascular disease, LDA – low dose aspirin, Om - omeprazole, D – diclofenac, Pl - placebo, Clopidr – Clopidrogel. Rab – rabeprazole, ASA – acetylsalicylic acid, CHD – coronary heart disease. Pant – pantoprazole, GB – gastric bleeding.

The spectrum of Action of Rebamipide in Diseases of the Gastrointestinal Tract

Currently, in foreign and domestic practice, rebamipide is used to prevent and treat drug-induced lesions of the upper and lower gastrointestinal tract when taking various ulcerative drugs such as NSAIDs, antithrombotic drugs, in the treatment of erosive and ulcerative lesions of the gastrointestinal tract, dyspepsia, gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), chronic gastritis (during antihelicobacter therapy and atrophic gastritis and also in order to prevent the

development of stomach cancer after eradication of Helicobacter pylori). The use of rebamipide for preventive purposes to prevent the effects of ulcerative drugs is based on cytoprotective effects, proven both in animal experiments and in clinical randomized double-blind placebo-controlled trials. So in the work of Tae Jun Kim et al. 9133 patients with osteoarthritis and rheumatoid arthritis who used NSAIDs for ≥1 month were studied, rebamipide was compared with proton pump inhibitors (PPIs) and histamine H2 receptor blockers (BH2RH). Rebamipide, as well as PPIs and BH2RH, were effective in reducing the risk of gastrointestinal injury when using NSAIDs [8].

The cytoprotective effect of Rebamipide is based on increased production of prostaglandins E2, mucus due to the induction of COX-2, antioxidant capture of free radicals, improvement of blood flow in the gastrointestinal mucosa, anti–inflammatory effect due to inhibition of neutrophil activity and expression of pro-inflammatory cytokines, restoration of impaired permeability of the epithelium of the gastrointestinal mucosa caused by taking NSAIDs, modulation of the gastrointestinal microbiome, thus acting for all elements of the gastrointestinal mucosa protection – preepithelial, epithelial and postepithelial.

In clinical practice, the occurrence of enteropathy and anemia caused by taking small doses of acetylsalicylic acid (ASA) is of great importance, since the prevalence of taking this drug to prevent cardiovascular and cerebrovascular diseases is very high. It is quite simple to determine various injuries of the upper and lower gastrointestinal tract by conducting an appropriate endoscopic examination, but it is more difficult to determine damage to the small intestine, which is possible only by using videocapsular enteroscopy. Damage to the small intestine according to capsule endoscopy varies depending on whether low-dose aspirin (from 50% to 95.5%) or non-selective NSAIDs (from 29% to 91%) or selective NSAIDs were used. (6.4% to 48.8%). However, convincing data on the differences has not been obtained. According to the results of the study by Toshio Watanabe and co-authors, when taking small doses of aspirin, damage to the small intestine mucosa occurs after 8 weeks in 91% of patients, and according to Edgardo Smecuol and co-authors, taking small doses of aspirin in healthy volunteers after 2 weeks led to damage to the small intestine in one in two, significantly fecal calprotectin was increased and the permeability of the small intestine mucosa was impaired significantly [9, 10]. According to a placebo-controlled study by Yasumasa Niwa and co-authors, rebamipide was significantly more effective than placebo in preventing the development of damage to the small intestine mucosa when taking NSAIDs (diclofenac) in healthy subjects according to capsule video endoscopy. There were no ulcers and/or bleeding in the group of healthy people taking rebamipide [11]. Double-blind randomized trials by Kazuhiro Mizukami et al., 2011 and 2012. in assessing the effectiveness of the preventive effect of rebamipide when taking low doses of aspirin, rebamipide was also highly effective in reducing damage to the ileum mucosa compared with placebo (differences in the groups were statistically significant after a week $p=0.0173$ and after 4 weeks $p=0.0266$) in the first study, and in the second the frequency of lower gastrointestinal symptoms was significantly lower than in the placebo group after 4 weeks, $p<0.0093$ [12,13]. A study by Shunji Fujimori and co-authors indicated that 50% of patients had damage to the small intestine mucosa when taking traditional NSAIDs and the preventive effect of rebamipide when taking NSAIDs [14].

In accordance with the recommendations of the Chinese Rheumatism Data Center and the Chinese Group for the Treatment and Research of Systemic Lupus Erythematosus, for the prevention and treatment of NSAID-induced gastrointestinal ulcers and their complications, it is necessary to evaluate the functions of the gastrointestinal tract and cardiovascular system before using NSAIDs, and the expediency of using PPIs and rebamipid [15].

The report of the multidisciplinary group on the use of NSAIDs and antiplatelet drugs in Asia in paragraphs 21 and 22 indicated the effectiveness of misoprostol and PPIs, in paragraph 23 there was insufficient evidence of histamine H2-receptor blockers in reducing the risk of bleeding when taking non-selective NSAIDs. Eradication of Helicobacter pylori reduces the risk of developing peptic ulcers in patients who are about to start long-term NSAID therapy (paragraph 27). In paragraph 28, it was stated that there is no evidence for mucoprotective drugs such as sucralfate and rebamipide in reducing the risk of upper gastrointestinal bleeding [16], but subsequent studies have proven the effectiveness of rebamipide in preventing the development of ulcers or erosions of the upper and lower gastrointestinal tract, as well as the development of bleeding induced by NSAIDs. Rebamipide is widely used in most Asian countries, and studies have been published that have proven the effectiveness of rebamipide in reducing damage to the gastrointestinal mucosa associated with NSAID use, as evidenced by the data presented in table 1, indicating the countries in which the studies were conducted. An interesting fact is that the more frequent appointment of gastroprotectors, including rebamipide, is consistent with the doctor's experience [17]. Review of data on side effects provided by the FDA (Food and Drug Administration) – the Inverse Event Reporting System (FAERS) – the largest database in the world, as well as in the Japan Adverse Drug Event Report (JADER) and the Pharmaceutical and Medical Equipment Agency - Pharmaceuticals and Medical Devices Agency (PMDA) They include data on all patients who have had side effects, for example, when taking NSAIDs, including small doses of aspirin or antithrombotic drugs, and not only from randomized clinical trials.

The results of the evaluation of the presented databases indicated a significant reduction in the risk of lower gastrointestinal tract damage when loxoprofen or diclofenac were taken together with rebamipide (n=2689, loxoprofen + rebamipide, OR = 1.15, 95% CI 0.88 – 1.51; n=568, diclofenac + rebamipide, OR = 1.28, 95% CI 0.82 – 2.01 – from the FAERS database; n=6102, loxoprofen + rebamipil, OR = 0.50, 95% CI 0.35 – 0.71; n=1539, diclofenac + rebamipide, OR = 0.43, 95% CI 0.27 – 0.67), thereby confirming the preventive effect of rebamipide damage to the lower gastrointestinal tract [18]. Shimada K, and colleagues analyzed the effect of antithrombotic drugs (ATD) on the occurrence of gastrointestinal bleeding when taking them according to the FAERS and JADER databases [19], which showed a significant effect of ATD on the occurrence of gastrointestinal bleeding, which requires appropriate monitoring and preventive treatment. Currently, there is a sufficient number of studies conducted in accordance with the requirements of evidence-based medicine to confirm the statistically significant

preventive effect of rebamipide when taking NSAIDs, including low-dose aspirin, as confirmed by the data from our meta-analysis. The use of rebamipide should begin on the first day of taking NSAIDs or small doses of aspirin, as evidence has been obtained of damage to the gastrointestinal mucosa such as petechiae after 2 hours, even more after 6 hours of taking small doses of aspirin (especially often in the upper part of the stomach and the arch), erosion after 24 hours, and even duodenal ulcers.

After reviewing all available resources for various search words on the chosen topic, we selected 26 studies that meet the criteria of evidence-based medicine. It is noteworthy that 23 of the 26 studies were conducted in Asia, mainly in Japan and Korea (see the table 1) [20-32,11-14,33-39]. These studies included comparisons of rebamipide and placebo – 11 studies, rebamipide and misoprostol – 2 studies, rebamipide + PPIs and Placebo + PPIs – 6 studies, rebamipide and antisecretory drugs (PPIs or histamine H2 receptor blocker) – 7 studies. In all the studies presented in Table 1, the compared groups did not have statistically significant differences in all criteria that could have an impact on the final results (average age, gender, and many others). When conducting a sensitive analysis, a study conducted by Thiago Gagliano-Jucal and co–authors in 2016 was excluded, which was due to inadequate use of the rebamipide dose in the study of 100 mg 2 times a day (does not comply with the instructions), which led to certain results - rebamipide did not protect against naproxen-induced damage to the gastric mucosa [29].

Table 2: Rebamipide versus placebo for the prevention of NSAID-induced gastrointestinal injury

Study	Number (n) Rebamipide/Placebo	Gastrointestinal Injuries Rebamipide/Placebo	Note
Naito Y, et al. 1998 [20],	10/10, Efficiency was assessed 7/ 10.	Gastric erosions 14% in the rebamipide group vs. 70% in the placebo group, p<0.05 (difference is significant). Gastric ulcers in 3 patients (only in the placebo group). Assessment by MLS.	The occurrence of symptoms was 43% versus 80% in the placebo group (the difference was not significant), but there was a downward trend in the Rebamipide group.
Kim H-K, et al. 2007 [21],	10/10. Efficiency was assessed 10/10.	In the placebo group, there were 3 ulcers (30%) and 0 (0%) in the rebamipide group. p=0.032. Assessment by MLS.	Blood flow impairment in the placebo group was correlated with skin damage, r=0.677, p=0.001.
Kawai T, et al. 2009 [22],	Efficiency was assessed 10/10	Multiple erosions in 1 of 9 (11.1%) in the rebamipide group versus 6 of 10 (60%) in the placebo group, p=0.024. Assessment of erythema, petechiae, erosions, and ulcers	The presence of petechiae or erythema was not significant between the groups. Rebamipide significantly prevented the development of gastrointestinal symptoms, 1 versus 9 cases, p=0.0094.
Ono S, et al. 2009 [23],	10/10 в 2 этапа. The effectiveness was evaluated by n=20 in the Pl group and n=20 in the Reb group.	Damage in the antrum – erosions in the rebamipide group 35% vs 55% in the placebo group, p=0.0393. Assessment by LS – Lanza score.	Rebamipide was more effective in preventing damage in the antrum od the stomach, but differences were not in the body and fundus of the stomach.
Nishida U, et al. 2011 [24],	10/10. The efficacy was evaluated in 10 patients in the placebo group and 10 patients in the Reb group.	0/2 erosions in the ileum 0% (rebamipide) vs. 20% (placebo). Differences in the number of Er, Pet, and Erit in the Reb and Pl groups, respectively: 0.0 ± 0.0, 8.6 ± 0.0 и 0.6 ± 0.0 vs 0.5 ± 2.7, 10.1 ± 53.6 и 1.0 ± 2.3. Assessment by MLS.	In the rebamipide group blood flow in the small intestine did not change unlike in the placebo group.
Hasegawa M, et al. 2013 [25],	The efficacy was evaluated in 65 patients: 31 in the rebamipide group and 34 in the placebo group.	0/6 ulcer - 0% versus 6/34 - 17.6%, p=0.0252.	Rebamipide is more effective than placebo in preventing stomach ulcers.

Tozawa K, et al. 2014 [27],	The efficacy was evaluated in 8 patients of group 1 (Pl + LDA), 7 patients of group 2 (Reb + LDA), 8 patients of group 3 (Pl + LDA + Clopidrogel), and 7 patients of group 4 (Reb + LDA + Clopidrogel).	Differences in the MLS between groups 1 and 2 are statistically significant, $p<0.05$. Differences in the MLS between groups 3 and 4 are statistically significant, $p<0.05$. In groups 1 and 3 the MLS increased significantly on day 14, $p<0.01$.	Rebamipide prevented skin damage induced by LDA or LDA combined with clopidrogel.
Pittayanon R, et al, 2019 [31],	The efficacy was evaluated in 42 patients with rebamipide and 41 patients with placebo.	ITT after 3 months of observation, the ulcer 11 out of 42 in the rebampide group – 26.2% vs 17 out of 41 in the placebo group – 41.5%. Ulcer > 5 mm in diameter in 2 of 42 (4.8%) in the rebamipide group vs 8 of 41 in the placebo group (19.5%), $p=0.04$. Per protocol – ulcer <5 mm in diameter 2/30 in the rebamipide group vs 8/20 in the placebo group, $p=0.03$	Rebamipide was significantly more effective than placebo in preventing the development of ulcers less than 5 mm in diameter. Rebamipide did not affect the antiplatelet effect.
Total	146/151	Mav 12.3% vs 42.0%, $p<0.001$.	Rebemipid was significantly more effective than placebo in preventing the development of erosions and ulcers.

MLS - modified Lanza score, Reb – rebamipide, Pl – placebo, Er - erosion, Pet - petechia, and Erit – erythema. Av - average

Analysis of included studies was performed in relation to the aim of using Rebamipide (prevention or treatment of NSAID-induced gastroenteropathia, application of rebamipide monotherapy^ comparison with misoprostole or antisecretorn undeclared preparation, libo conduct of combination therapies rebamipid and IPA). The evaluation of the preventive effect of Rebamipide was carried out in comparison with placebo according to 8 randomized controlled trials, of which only one was a randomized discovery, but blinded by conal results, all remaining randomized double-blind placebo-controlled trials. The results of a meta-analysis with an assessment of effectiveness in preventing the development of gastrointestinal injuries are presented in Table 2. The results of the evaluative meta-analysis of the preventative actions of the Rebamipida in the Apostille that are credible clinically relevant in the behaviorofjective ego as in the warning and the development of the desired-specific-cishchehns of the Apostille damage, TAC and decreased symptomatic quantities. It is especially necessary to emphasize the high importance of the preventive action of Rebamipide in relation to damage to the small intestine, since the effective NSAID-induced esophagogastroduodenopathies and H2-receptor blockers histamine do not act on the small intestine due to the absence of the main factor that it affects. It should also be noted that of the 23 evaluated studies, 14 included healthy subjects, but damage to the gastrointestinal mucosa (corrosion and/or ulcers) developed from 0% to 35% when taking rebamipide (Mcp = 15.2%) and from 17.6% to 70% when taking placebo (Mcp = 48.9%), $p<0.001$.

The analysis of the included studies was carried out depending on the purpose of taking rebamipide (prevention or treatment of NSAID-induced gastroenteropathies, the use of rebagit monotherapy, comparison with misoprostol or an antisecretory drug, or combination therapy with rebamipide and PPIs). The evaluation of the preventive effect of Rebamipide was carried out in comparison with placebo according to the data of 8 randomized controlled trials, of which only one was randomized open, but blinded by the final results, all the others were randomized double-blind placebo-controlled trials. The results of the meta-analysis with an assessment of the effectiveness in preventing the development of gastrointestinal injuries are presented in Table 2. The results of a meta-analysis of the preventive effect of Rebamipide revealed reliable clinically significant effectiveness in preventing the development of gastrointestinal damage and reducing the number of symptoms. The high importance of the preventive action of Rebamipide against damage to the small intestine should be especially emphasized, since PPIs and histamine H2 receptor blockers, effective for preventing damage to NSAIDs-induced esophagogastroduodenopathies, do not act on the small intestine due to the absence of the main factor they affect. It should also be noted that of the 23 evaluated studies, 14 included healthy subjects, but damage to the gastrointestinal mucosa (erosion and/or ulcers) developed from 0% to 35 when taking rebamipide (Mcp = 15.2%) and from 17.6% to 70% when taking placebo (Mcp = 48.9%), $p<0.001$.

Table 3: Efficacy of rebamipide in the treatment of small intestinal injury induced by low doses of aspirin

Study	Quantity (n) Rebamipide/Placebo	Reduction of small intestinal damage Rebamipide/Placebo	Note
Kurokawa S, et al. 2014 [26],	61 (rebamipide - 31, placebo -30). Reb 100 mg t.i.d - 4 weeks. The efficacy was evaluated in 31 patients in the rebamipide group and in 30 patients in the placebo group.	-3.2 ± 4.1 vs 2.1 ± 3.9 (p<0.0001). -0.5 ± 1.6 vs 0.1 ± 0.7 (p=0.024). 0.06 ± 0.36 vs 0.27 ± 0.34 (p=0.0005).	Statistically significantly, the number of small intestinal erosions is lower in the rebamipide group. Changes in the number of ulcers in favor of rebamipide. Improvement in nutritional status (total protein levels did not decrease compared to placebo).
Watanabe T, et al. 2015 [29],	38 (25 received rebampide; 13 received placebo). Rebampide 300 mg 3 times a day for 8 weeks.	p=0.046. p=0.13 (differences NS, but with a tendency towards a higher score when taking rebamipide).	The number of small intestinal lesions decreased significantly. Complete healing was observed in 32% of patients taking rebamipide, compared to 7.7% in the placebo group.
Total	99	pav=0.023	The differences in the therapeutic effect of rebamipide and placebo in reducing the number of small intestinal lesions are significant.

Reb – rebamipide. NS – not significant. Av – average.

Regarding the therapeutic effect of Rebamipide in the treatment of NSAID-associated esophagogastroenteropathies, 2 studies were selected, in one of which patients with enteropathy caused by low-dose acetylsalicylic acid (ASA) took Rebamipide 100 mg 3 times daily or placebo (Kurokawa S, et al. 2014, randomized, double-blind placebo—controlled research, n=61). Statistically significantly, the number of small intestinal erosions was lower after 4 weeks with Rebamipide than in the placebo group, p<0.0001; changes in the number of ulcers in the small intestine were also in favor of Rebamipide, p=0.024. [26]. Rebamipide not only had a healing effect in patients, but also improved nutritional status (the level of total protein in the blood did not decrease in comparison with placebo). In another randomized, double-blind, placebo-controlled study, Watanabe T, et al. 2015, patients with cardiovascular or cerebrovascular pathology and established small intestinal enteropathy caused by low-dose aspirin took Rebamipid 300 mg 3 times daily or placebo (n=38). Taking Rebamipide reduced the number of small intestine injuries statistically significantly compared with placebo, p=0.046. Complete healing was noted in the Rebamipide group in 32% versus 7.7% in the placebo group (the difference was not significant, p=0.13) [29]. Based on the analysis of these studies, it can be argued that Rebamipide has a statistically significant therapeutic effect in patients with small intestinal enteropathy caused by taking small doses of ASA to reduce the number of such injuries compared with placebo.

When monitoring patients with NSAID-induced enteropathy, we observed a significant positive trend in the intestinal microbiota according to Colonoflor Premium – an increase in lactobacilli and a decrease in bacteroids, in contrast to PPIs. It is important to note that with the proven effect of rebamipide, PPIs not only do not prevent the development of NSAID enteropathies, but also increase the risk of such events when taking PPIs, including small intestinal bleeding [32-34].

Table 4: Rebamipide versus Misopristol for the prevention of NSAID-induced gastrointestinal injuries

Study	Quantity (n) Rebamipide/Placebo	Reduction of small intestinal damage Rebamipide/ Placebo	Dispeptic symptoms Rebamipide/Misoprostol
Park S-H, et al. 2007[35],	207/203 Efficiency was assessed 176/156	Gastric ulcer and Duodenal ulcer 8/7, p=0.976 (NS)	The clinical severity of symptoms in the Reb group was significantly lower after 12 weeks of treatment, p=0.0083. Compliance in the Reb group was significantly higher 174/155, p=0.0349. AE, p=0.0083.
Kim JH, et al. 2014 [36],	242/237 Efficiency was assessed У 217/193	Gastric ulcer and Duodenal ulcer 49/52, p=0.6497 (NS)	The severity of symptoms in the Reb group is significantly lower after 12 weeks of treatment, p=0.0002 Drug discontinuation 25/44, p=0.0103. The use of antacids is higher when taking Misoprostol, p=0.0258. AE, p=0.0746

Total	393/349	Gastric ulcer and Duodenal ulcer 57/59, p=0.8129 (NS)	Clinical severity of symptoms is lower in the Rebamipide group, p=0.0043. AE is lower in the Rebamipide group, p=0.042

NS – not significant, Reb – rebamipide, AE – adverse event.

To evaluate the comparison of rebamipide and misoprostol, 2 randomized, double-blind controlled trials were selected (see table 4). The results of the analysis indicated significantly equal effectiveness of the preventive action of rebamipide and misoprostol, but adverse events occurred significantly more often when taking misoprostol, more often drug withdrawal and taking an additional antacid drug, worse compliance than in the rebamipid group [35,36].

Table 5: Comparative efficacy of Rebamipide and Placebo in combination with PPIs in preventing the development of NSAID-induced gastrointestinal injuries.

Study	n	Gastrointestinal damage	Note
Niwa Y, et al. 2008 [11],	10/10. Efficiency was assessed 10 for each group.	In the group of Placebo injuries 8/10 (80%), in the group of Rebamipide 2/10 (20%), p=0.023. 2 cases of ulceration and 1 case of bleeding in the placebo group, compared to 0 in the Rebamipide.	Rebamipide was significantly better at preventing damage caused by diclofenac than a placebo.
Mizukami K, et al. 2011 [12],	11, Efficiency was assessed 11 in Rebamipide group and 12 in Placebo group.	In the placebo group, small bowel damage was significantly more common at 1 and 4 weeks compared to the rebampide group, p=0.0173 and p=0.0266.	Rebamipide was significantly better at preventing damage caused by LDA than a placebo.
Mizukami K, et al. 2012 [13],	12, Efficiency was assessed 12 in Rebamipide group and 12 in Placebo group.	Symptoms of the lower gastrointestinal tract were significantly less common in the rebampide group – OR 0.08, 95% CI: 0.01 – 0.71, p<0.0093.	Rebamipide was significantly better at preventing symptoms from the lower gastrointestinal tract.
Fujimori S, et al. 2011 [14],	72, NSAID + Om + Pl – 38; NSAID + Om + Reb – 34.	The number of injuries was 8.9 in the NSAID + Reb + Om group, compared to 25 in the NSAID +Pl + Om group, p=0.038.	The inclusion of rebamipide significantly reduced the number of small intestine injuries.
Ito Y, et al, et al. 2013 [37],	10, Efficiency was assessed 10 patients: Pl + Diclof + Om and 10 patients: Reb + Diclof + Om.	Bleeding in 2 in the placebo group and in 1 in the rebampide group. Damage to the small intestine is the same in both groups – 6 out of 10 (NS).	The differences in small intestine permeability were not statistically significant.
Mbarki M, et al. 2017 [38],	102 patients with cardiovascular disease, 64.7 years old, 55 men and 47 women. n= 37 (ASA group), n=33 (ASA + PPI group), n=32 (ASA + PPI + Rebamipid group).	Gastric ulcers in groups 1, 2 and 3 were 6%, 2% and 0%, respectively. Gastric erosions in groups 1, 2 and 3 were 26%, 14% and 0%. Duodenal erosions in groups 1, 2 and 3 were 3.8%, 7.85 and 3.9%. The differences between groups 1 and 3 are statistically significant when comparing the presence of stomach ulcers, p<0.024, stomach erosions, p<0.002, and duodenum erosions, p<0.026.	The levels of the inflammatory mediator LTB4 were highest in the ASA group at 50 ng/mL, and lowest in the rebamipide + pantoprazole group at 18 mg/mL. The levels of prostaglandin E2 were lowest in the ASA group at 1.4 pg/mL, and highest in the rebumipide + pantoprazole group at 1.6 ng/mL. Combined therapy with PPIs and Rebamipide is effective in preventing stomach and duodenal ulcers and erosions when ASA is taken.

NSAID – nonsteroid anti-inflammatory drug, Om – omeprazole, Reb – rebamipide, Pl – placebo, Diclof – diclofenac, LDA – low dose aspirin. ASA – acethylsalicylic acid, NS – not significant.

The following meta-analysis (see Table 5) was performed by us in relation to the comparison of NSAID intake plus Rebamipide + Omeprazole and NSAIDs + Placebo. 6 studies were evaluated, 5 of them randomized, double-blind, placebo-controlled. In 5 out of 6 studies, the inclusion of rebamipide in the regimen reduced the amount of damage to the gastrointestinal mucosa, and in only one study, Ito Y and co-authors, the effectiveness of rebamipide and placebo had no significant differences [11-14,37,38]. A study by

Mizukami K, et al, 2012 determined only the dynamics of symptoms from the upper and lower gastrointestinal tract.

Table 6: Efficacy of rebamipide and antisecretory drugs in the prevention and treatment of NSAID-induced gastrointestinal injuries

Study	n	Gastrointestinal damage	Note
Ota K, et al. 2016 [39].	45. The efficacy was evaluated in: Group A: LDA + Om 10 mg (n=15); Group B: LDA + Reb 300 mg (n=15); Group C: LDA + Reb 900 mg (n=15).	The differences between the groups were not statistically significant, but the trend was of dose-dependent prevention of Rebamipide. In group C gastroduodenal injuries there were not – 0/15 (0%). In group B injuries there were 2/15 (13.3%) and in group A injuries there were 4/15 (26.7%) – NS, but trend there was a towards improvement in MLS in all groups. Significant differences there were not between the groups in terms of small intestinal injures.	The effect of Rebamipide 300 mg/day was not inferior to rebamipide 900 mg /day. In group A calprotectin significantly increased, p=0.004, in groups B and C calprotectin did not tend to increase (NS), p=0.884 and p=0.438). Hidden blood in the stool in group A – 1/14; B – 0/15 and C – 0/14 (NS).
Tkach S., et al., 2017 [30].	The effectiveness was evaluated in patients: 1-st group - Diclofenac + Omeprazole 42 patients. 2-nd group - Diclofenac + Rebamipide 46 patients. 3-rd group - Diclofenac 30 patients.	Total number of stomack and duodenal ulcers. 1-st: 4 – 9.5%; 2-nd: 4 – 10.5%; 3-rd: 8 – 26%. The differences between 1-st and 2-nd groups are not significant, but they are significantly less common in the 3-rd group, h=0.037. Gastroduodenal erosions according to the Lanza score in the 1-st, 2-nd and 3-rd groups after 1 month: 19%, 23.9% and 46.6%, p=0.027. NS between 1-st and 2-nd groups, but significantly less common in the 3-rd group, p=0.017.	The adverse events in groups 1 and 2 did not differ, except for diarrhea, which was significantly less common in group 3. Two patients in group 3 experienced gastroduodenal bleeding.
Oh DJ, et al. 2022 [40].	40. The efficacy was evaluated in 15 patients in group 1: Meloxicam + Rebamipide and in 18 patients in group 2: Meloxicam + Lansoprazole.	No gastric ulcers in either group after 12 weeks. In the 1-st group small intestinal damage was 1.75 and 4.00 in the control group. Multiple erosions were 20% in the Rebamipide group and 40% in the Lancoprazole group, but the differences were not statistically significant (Assessment by MLS).	The differences in AE were significant: 31.5% in the rebampide group versus 65% in the control group, p=0.036. The intensity of gastrointestinal symptoms did not differ significantly between the groups. Rebampide was as effective as Lansoprazole, but it was more safer.
Yamamoto T, et al. 2010 [41].	542 patients who took LDA for 1 month. The presence of erosions and gastroduodenal lesions was assessed in 530 patients.	In therapy with PPIs/H2-blocker + Rebamipide (n=27) of bleeding 0, erosions and ulcers 4 (14.8%) vs 38.1% when taking PPIs/H2-blocker + MD, p<0.05.	Rebamipide increases the effectiveness of preventive therapy with an antisecretory drug, unlike any other mucoprotective drug.
Jia R-J, et al. 2022 [42].	360 patients with dual antiplatelet therapy: LDA + clopidrogel. The efficacy was evaluated in 360 patients. Group 1 (n=90): LDA 100 mg/day + Clopidrogel 75 mg/day; Group 2 (n=90): LDA + Clopidrogel + Rab 20 mg/day; Group 3 (n=90): LDA + Clopidrogel + Reb 100 mg 3 times a day; Group 4 (n=90): LDA + Clopidrogel + Rab + Reb.	Bleeding was observed in groups 1, 2, 3, and 4, respectively: 11.1%, 3.3%, 8.9%, and 1.1%. The differences are statistically significant, p<0.05. The differences between groups 1 and 2, groups 1 and 4, and groups 3 and 4 are statistically significant, p<0.05.	The severity of upper gastrointestinal bleeding was significantly lower in the rabeprazole and rabeprazole + rebumipide groups than in the control group (LDA + clopidrogel). Treatment with rabeprazole or rabeprazole + rebumipide may reduce the risk of upper gastrointestinal bleeding. The combination of rabeprazole and rebumipide was the most effective.

Naito Y, et al. 2008 [43].	12. The efficacy was evaluated in 12 patients who took Indomethacin + Rebamipide and in 12 patients who took Indometacin + Famotidin.	Symptoms in 7 of 12 in the rebamipide group – 58% va 75% in famotidine group (9/12) – NS. Injuires of gastric mucosa – 42% in rebamipide group - 5/12 vs 42% in famotidine group – 5/12 when comparing all degrees of MLS. 0 ulcers in both groups. Assessment by MLS.	Rebamipide was as effective as famotidine in preventing damage to the gastric mucosa.
Yamao J-I, et al. 2006 [44].	112. The efficacy of n=55 rebamipide and n=57 famotidine in patients taking NSAIDs was evaluated. Famotidine 20 mg/day; Rebamipide 300 mg/day.	The number of lesions decreased significantly in the famotidine group ($p<0.001$), but not in the rebumipide group ($p=0.478$). Assessment by MLS. The changes in the famotidine group versus the rebamipide group were statistically significant, $p=0.002$	Famotidine was more effective in the treatment of NSAID-induced gastric mucosal lesions, Complete healing in the Famotidine group was 45.6% versus 18.2% in the Rebamipide group.

LDA – low dose aspirin, Om – omeprazole, SII – small intestinum injuries, MLS - Modified Lanza Score. AE - adverse event, GII – gastrointestinum injuries, MD – mucoprotective drug, Reb – rebamipide, Rab – rabeprazole, NS – not significantly, Rab – rabeprazole.

The direct comparison of rebamipide and PPIs, rebamipide and histamine H2 receptor blocker was evaluated in seven studies [30,39-44]. When comparing rebamipide and PPIs (omeprazole or lansoprazole), no significant differences were found. In a study by Yamamoto T, et al., the efficacy of rebamipide was compared with PPIs or a histamine H2 receptor blocker in patients taking low-dose aspirin. Of the 530 patients, 25 had bleeding (3.7%) and 192 had damage to the gastrointestinal mucosa (36.2%). Only taking PPIs reduced the number of bleeds, $p<0.05$. Gastroduodenal mucosal lesions were associated with the presence of Helicobacter pylori (OR 2.14, CI 95%, $p<0.01$), taking PPIs (OR 0.38, CI 95%, $p<0.01$). Combination therapy with PPIs or BH2RH plus rebamipide was associated with fewer bleeds (0 out of 22 in patients with PPIs + Rebamipide, 0 out of 5 in patients with BH2RH + Rebamipide) and gastrointestinal injuries, 3 erosions and 1 ulcer out of 22 in the PPIs + Rebamipide group and 1 erosion and 0 ulcers in the BH2RH + Rebamipide group. The differences are significant when comparing the PPIs/H2-blocker + Rebamipid groups versus PPIs/BH2RH, $p<0.05$. Rebamipide has the property not only to prevent damage to the stomach, but also to the intestines. In the study by Naito Y and co-authors, it was proved that rebamipide is not inferior in effectiveness to famotidine, however, in the study by Yamao J-I and co-authors, famotidine was found to be more effective than rebamipide (see Table 6).

Unlike rebamipide, taking PPIs according to a systemic meta-analysis conducted by Zhang X and co–authors, concomitant use of PPIs with NSAIDs significantly increased the frequency and number of endoscopically verified small intestinal lesions (frequency: Odds ratio – OR = 3.00; 95% Confidence interval - CI: 1.74 - 5.16; number of: The average difference was AD = 2.30; 95% CI: 0.61 – 3.99 and decreased hemoglobin level AD =-0.50 g/dL; 95% CI: 0.88 – 0.12), but the risk of small intestine bleeding did not change (OR = 1.24; 95% CI: 0.80 – 1.92). Moreover, PPIs significantly increased the incidence of small intestinal injury in patients taking non–selective NSAIDs (OR = 7.05; 95% CI: 4.70 - 10.59) [45].

The meta-analysis by Choe Y and co-authors included 18 randomized controlled trials in which patients used NSAIDs and various mucoprotective drugs [46]. Conclusion of the meta-analysis: rebamipid is recognized as a cytoprotective drug that can protect small intestinal damage. A meta-analysis by Ramos J, et al. evaluated the efficacy of rebamipide against PPIs, BH2RH, and misoprostol in randomized controlled trials. The authors conclude that there is currently insufficient evidence in favor of the preventive effect of gastroduodenal lesions induced by the NSAID rebamipide [47]. A systematic review and meta-analysis by Cion RI, and co-authors included 13 studies. A generalized analysis showed that rebamipide significantly reduced the incidence of NSAID-induced gastrointestinal injury compared with placebo, $p<0.00001$. Rebamipide was comparable to PPIs in preventing the development of NSAID-induced lesions of the gastrointestinal mucosa [48]. A study by Yamate S and co-authors revealed that the constant intake of rebamipide significantly reduced the risk of bleeding from the upper gastrointestinal tract in new NSAID users with osteoarthritis or lumbar pain without risk factors [49]. A systematic review and meta–analysis by Zhang S and co-authors (15 randomized controlled trials) revealed that rebamipide is effective and safe for protection against NSAID-induced gastroduodenal lesions. Rebamipide was equal or not higher to strategies involving PPIs, BH2RH, and misoprostol. Rebamipide was especially effective against small intestinal damage, $p<0.05$ when compared with placebo, in the absence of serious adverse events [50]. An analysis of small intestinal bleeding from the jejunum and ileum below the Treitz ligament caused by NSAID use and conducted by Deng Y-H and co-authors revealed that PPIs do not have a significant effect on such bleeding, while rebamipide and probiotics have a preventive effect on small intestinal bleeding associated with NSAID use [51]. The analysis was conducted according to the FDA Inverse Event Reporting System (FAERS) and the Japanese Side Effects Report (JADER). In a meta-analysis by Zhang W-t and co-authors, it was shown that the best preventive effect when taking aspirin is a combination of omeprazole and rebamipide [52]. The meta-analysis of randomized trials by Scally B and co-authors included 848 studies of gastroprotectors against controls: 580 preventive studies (110626 participants), 2233 treatment (24033 participants) and 36 studies for the treatment of acute bleeding from the upper gastrointestinal tract (7826 participants) [53]. A meta-analysis by Brigitta Teutsch

also confirmed the effectiveness of rebamipide in the prevention and treatment of NSAID-induced small intestinal injury [54]. Another proof in favor of rebamipide is a study by Kim J.E., et al., which showed that rebamipide prevents a drop in hemoglobin associated with drugs that damage the mucosa comparable to PPIs, but is more effective than BH2RH [55].

Manish Kak's work on the possibilities of rebamipide in the prevention and healing of the gastric mucosa should also be noted, emphasizing the importance of including rebamipide in the gastroprotective regimen when taking NSAIDs, especially to prevent gastrointestinal bleeding, damage to the gastrointestinal mucosa, and stomach cancer [56]. In accordance with the recommendations for peptic ulcers caused by medication published in the Korean Journal of Gastroenterology, misoprostol was excluded from the recommended list of protective agents, taking into account the side effects [57]. According to Rostom A, and co-authors (Cochrane Database Syst Rev), misoprostol reduced the risk of peptic ulcer complications, but only at a dose of 800 μg per day, but at this dose it was significantly more likely to cause adverse events such as diarrhea [58,59].

Evaluating potential strategies in preventing NSAID-associated side effects in the lower gastrointestinal tract, Chuan-Guo Guo, Wai K Leung conclude that the use of misoprostol leads to a large number of side effects such as abdominal pain, nausea, vomiting, diarrhea, and the use is accompanied by frequent drug withdrawal. The use of PPIs is effective in reducing the risk of damage to the upper gastrointestinal tract, but may increase the risk of NSAID-induced small intestinal injury and bleeding, which is confirmed by other researchers [60-62]. Unlike PPIs, rebamipide has proven to be effective and safe in the prevention and treatment of NSAID-induced enteropathies. [11-14,26,29,35,48]. In patients with rheumatoid arthritis who take PPIs, the intestinal microbiota differs significantly from those taking rebamipide, $p<0.0005$ (the content of streptococci and microorganisms involved in the production of virulence factors is significantly increased, unlike rebamipide, the content of Clostridium boltea is increased) [63]. Hypochlorhydria caused by the use of PPIs according to a meta-analysis of studies conducted using the sequencing technique, it was found that PPIs caused by PPIs contributes to the colonization of more distant parts of the digestive tract by the microbiota of the upper gastrointestinal tract [64].

Table 7: Characteristics of included metaanalyses

Study	n	Characteristic	Conclusion
Zhang X, et al, 2023 [45].	14 randomized controlled studies	PPI + NSAID vs NSAID	PPIs were significantly more likely to cause small intestinal damage when taking non–selective NSAIDs (OR = 7.05; 95% CI: 4.70 – 10.59) and selective NSAIDs (OR = 4.00; 95% CI: 1.18 - 13.60) compared with taking only selective NSAIDs.
Choe Y, et al, 2024 [46].	18 randomized controlled studies	NSAID and different MD	Rebamipide is recognized as a cytoprotective drug that can protect against small intestinal injuries.
Ramos J, et al, 2012 [47].	68 articles, 11 from Otsuka, and 19 unpublished studies, of which only 6 met the inclusion criteria.	Rebamipide versus PPI, BH2RH, Misoprostol	At now insufficient data there is on the preventive effect of rebamipide on gastroduodenal damage induced by NSAID.
Cion R.I., et al, 2025 [48].	13 randomized controlled studies	Rebamipide versus Placebo, PPI.	Rebamipide significantly reduced the incidence of NSAID-induced gastrointestinal damage compared to placebo, p=0.00001. Rebamipide was comparable to PPIs in preventing the development of NSAID-induced gastrointestinal damage.
Yamate S, et al, 2024 [49].	67561. 215 cases met the inclusion criteria, and 1516 were controls.	Regular and irregular intake of rebamipide was evaluated.	Rebamipide reduced the risk of upper gastrointestinal bleeding in new users of NSAIDs with OA or lumbar pain without risk factors.
Zhang S, et al, 2013 [50].	15 randomized controlled studies (965 participants)	Rebamipide versus Placebo, PPI, BH2RH, Misoprostol.	Rebamipide was equal to or lower than PPI, BH2RH. Особенно Rebamipide was effective especially against small intestinal injuries when compared with Placebo, $p<0.05$. The serious adverse events there are not.
Deng Y-H, et al, 2025 [51].	According to the data FAERS и JADER.	The effectiveness of PPIs, Rebamipide and probiotics in preventing small bowel bleeding from the jejunum and ileum was evaluated.	Rebamipide and probiotics may have a preventive effect on NSAID-associated small bowel bleeding, but PPIs do not have a significant effect.
Zhang W-t, et al, 2021 [52].	10 randomized controlled studies	Evaluation of the preventive effect PPIs, rebamipide, and misoprostol when taking aspirin.	The combination of omeprazole and rebamipide has the best preventive effect when taking aspirin.

Scally B, et al, 2018 [53].	849 studies (580 prevention, 233 healing and 36 for treatment of acute upper gastrointestinal bleeding)	Evaluation of one gastroprotector against another, against control.	Any gastroprotector reduces the frequency of bleeding.
Teutsch B, et al. 2021 [54].	18 randomized controlled studies	Evaluation of the effectiveness of prevention and treatment of NSAID-induced small intestinal enteropathy.	MD, including rebamipide, reduced the number of small intestinal injuries (OR = 0.38; DI: 0.16 – 0.93) and was particularly effective in the treatment of such injuries (OR = 5.39, DI: 2.79 – 10.42).
Kim J. Y., et al, 2024 [55].	195817 patients taking drugs that damage the gastrointestinal mucosa, including NSAIDs, ATD, and anticoagulants. n=95608 taking only mucosal-damaging drugs. n=48668 taking protective drugs.	Rebamipide versus PPI, BH2RH.	Rebamipide prevents a drop in hemoglobin associated with drugs that damage the gastrointestinal mucosa, which is comparable to PPIs but more effective than BH2RH.

PPI – proton pump inhibitor, NSAID – nonsteroid antiinflammatory drug, MD – mucoprotective drug, BH2RH – blocator H2-receptor histamine, OA – osteoarthritis,

In recent years, work has begun to appear on the preventive effect of potassium-competitive acid blockers (P-CAB). One of them was compared the assessment of the preventive effect of NSAID use in a multicentric, randomized, double-blind, placebo-controlled trial. In 3 groups, patients on the background of long-term NSAID use took, respectively, in group 1 - lansoprazole 15 mg + placebo (n=121), in group 2 – vonoprazane 10 mg + placebo (n=148) and in group 3 – vonoprazane 20 mg + placebo (n=137) for 24 weeks. Vonoprazane was more effective in preventing peptic ulcer at any dose versus lansoprazole 15 mg, $p<0.001$[65]. Despite the great importance of taking aspirin in the occurrence of gastrointestinal bleeding, only 0.12% of medical prescriptions combined PPIs + a mucoprotective drug, while most often only PPIs were prescribed, and rebamipide with a proven base of efficacy was less common than almost all other mucoprotective drugs (with the exception of sucralfate), although it is the safest of them and the most effective [66].

In the future, studies on the combined use of rebamipide and potassium-competitive proton pump blockers for the treatment and prevention of NSAID-induced esophagogastroenteropathies are required.

Thus, based on the latest data presented on the prevention and treatment of NSAID-induced gastrointestinal mucosal lesions from our meta-analysis, previously conducted meta-analyses [45-55], recommendations of the RGA, consensus of experts 2024: rational use of NSAIDs by the Association of Rheumatologists of Russia, the Russian Interregional Society for the Study of Pain, the Russian Scientific Medical Society of Therapists, the Association of Traumatologists-Orthopedists of Russia, American College of Gastroenterologists (Positions for the treatment of NSAID-related ulcerative complications), Expert consensus document on reducing gastrointestinal risks of antiplatelet therapy and the use of NSAIDs by the American College of Cardiology, the International NSAID Consensus Group, the European Alliance of Rheumatology Associations, Joint Positions ACCF/ACG/AHA – the American College of Cardiology/American College of Gastroenterology/American Association of Cardiology, the position of the American Heart Association, the positions of the International Society for Osteoarthritis Research, the positions of the American College of Rheumatology, the Canadian Consensus, the consensus of the Institute of the American Gastroenterological Association (AGA), the Mexican Consensus for the Diagnosis, Treatment and Prevention of NSAID-induced Gastropathy and Enteropathy [67-79] in accordance with determining the degree of recommendations and the level of evidence, the recommendations used in most of the recommendations should be recognized as correct and mandatory for the prevention and treatment of NSAID-induced

Esophagogastroenterocolonopathies:

- Consider the risk of gastrointestinal complications before prescribing NSAIDs.
  Level of evidence 1. Validity of recommendation A.
- Prescribing safer NSAIDs with the lowest risk of gastrointestinal damage and dyspepsia.
  Level of evidence 1. Validity of recommendation A.
- The combination of PPIs and rebamipide has the strongest preventive effect against the development of gastrointestinal tract damage.
  Level of evidence 1. Validity of recommendation A.
- Rebamipide has a therapeutic effect in all NSAID-associated gastrointestinal injuries, especially significant in lower gastrointestinal tract injuries, and should be prescribed from the first day of taking NSAIDs.
  Level of evidence 1. Validity of recommendation A.
- The safest mucoprotective drug at this stage is rebamipid.
  Level of evidence 1. Validity of recommendation A.

Proof level

1. The level of evidence strongly supports the recommendation.
2. The level of evidence supports the recommendation.
3. The level of evidence in favor of the recommendation is ambiguous.
4. The level of evidence does not support the recommendation.

Validity of Recommendations

A. Convincing evidence is formulated by numerous published, well-controlled randomized trials or well-designed systematic meta-analysis.
B. Convincing evidence from a published, randomized, controlled trial based on equality, or data from published,

well-planned cohort studies or comparable case-control studies.

C. Consensus of opinions of reputable experts based on clinical data or the results of well-planned, but uncontrolled or non-randomized clinical trials.

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